Investigation of aminotetralins as novel opioid receptor antagonists

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INVESTIGATION OF AMINOTETRALINS AS NOVEL OPIOID RECEPTOR ANTAGONISTS

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ABSTRACT

There has been much evidence in recent years to suggest that the κ opioid receptor plays a significant role in mediating a number of behavioural disorders including drug abuse and depression. Previous *in vitro* evaluation in the group of secondary and tertiary amines derived from 2-amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol showed that all behaved as pure opioid antagonists. These findings prompted further synthetic and pharmacological investigations of this scaffold, with the eventual aim of developing a short-acting selective opioid antagonist to further probe the κ receptor.

Using molecular modelling, a series of ligands were designed based on a previously prepared *N*-cinnamyl analogue but incorporating a second basic nitrogen intended to mimic the N17' nitrogen of norBNI and increase κ selectivity. Synthesis and pharmacological evaluation of the key intermediates revealed that the *ortho*-NH_2 derivative possessed the greatest κ affinity and antagonist potency, although the corresponding NO_2 analogue also exhibited high κ antagonist potency in the functional assay. Many of the synthetic steps were optimised and an improved protocol for the preparation of 7-methoxytetralone was developed.

Based on findings that aminotetralins possessing certain two-atom chains at the 3-position display high opioid receptor affinity, a second series of *N*-substituted ligands utilising an aminotetralin scaffold bearing a 3-OCH_3 group were synthesised which included an improved method for the hydride reduction of an oxime to aziridine. Preliminary pharmacological results indicate a considerable gain in opioid receptor binding whilst retaining pure antagonist activity; a novel selective κ antagonist ligand was also identified.

The encouraging results of the 3-OCH_3 analogues prompted investigation of a third series of ligands bearing 3-amino substituents, in order to evaluate the effect of an additional basic group in the scaffold. A synthetic route was devised which made use of a 'nosyl' group to activate the aziridine and introduce the desired 'address' side-chain. The 3-pyrrolidino analogue was successfully prepared by this method and it is anticipated that the route is flexible enough to allow a diverse range of analogues to be prepared in due course.

Finally, the preparation of a novel alkene intermediate utilising a cyclisation strategy was briefly investigated with the aim of identifying a synthetic route to future series of ligands which is efficient, economical and environmentally friendly.

ACKNOWLEDGEMENTS

I am indebted to a great many people for enabling me to retain my general sanity during the past three years or so in Bath. First and foremost I would like to thank my supervisor, Dr. Steve Husbands, for his good humour, enduring patience and always being available for advice and reassurance on all matters chemical or otherwise. Thanks must also go to Dr. John Lewis for his professional input and guiding the project in the right direction.

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ABBREVIATIONS

Ar	aromatic group
BOC	*tert*-butoxycarbonyl
br	broad
cAMP	cyclic-adenosine monophosphate
Cbz	carbobenzoxy
CPM	cyclopropylmethyl
CREB	cAMP-response-element-binding protein
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DOR	delta opioid receptor
EI	electron impact
Et	ethyl
EtOH	ethanol
eq	equivalent
FAB	fast atom bombardment
GTP	guanosine triphosphate
hr	hour
Hz	hertz
J	coupling constant
KOR	kappa opioid receptor
m	multiplet
M	moles per litre
Me	methyl
MeOH	methanol
MHz	megahertz

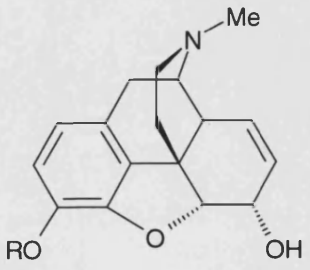
µl	microlitre(s)
ml	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MOR	mu opioid receptor
m.p.	melting point
mRNA	messenger ribonucleic acid
MS	mass spectrometry
m/z	mass to charge ratio
NAc	nucleus accumbens
NMR	nuclear magnetic resonance
Ns	nosyl (nitrobenzenesulfonyl)
norBNI	norbinaltorphimine
Nuc	nucleophile
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
psi	pounds per square inch
q	quartet
quint	quintet
RAVE	relative activity versus endocytosis
R_f	retention factor
rflx	reflux
RT	room temperature
s	singlet
SMEAH	sodium bis(2-methoxyethoxy)aluminium hydride
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	toluenesulfonyl
UV	ultra-violet

CHAPTER 1
INTRODUCTION

1.1 History of opioid research

The medicinal and recreational properties of opium, the juice extracted from the ripe seed capsules of the poppy *papaver somniferum*, have been known to humans for almost 6000 years.[1] Early records show that the poppy was first cultivated by the Sumerians in the area now known as the Middle East, where it was used principally for its euphoric effects. Its use spread quickly throughout the Egyptian empire and subsequently to the Greeks, who were the first to discover its powerful narcotic properties.[1-3] By 460BC, the Greek physician Hippocrates was administering opium for a whole range of complaints, from headaches and coughing to asthma and melancholy.[3] Opium was not introduced to Britain until the 17th century, where its use became widespread and addiction to it acquired a certain social cachet.[4] Towards the end of the 19th century, however, the use of the hypodermic syringe and needle saw the habit take on a more sinister significance.[1,2]

The first investigation into the constituent alkaloids of opium was carried out by Sertürner in 1806 who discovered morphine (**1**) by dissolving opium in acid and neutralising with ammonia.[1,5] Morphine, together with the later isolated codeine (**2**) and thebaine, comprise one of the two main classes of compound from opium: the opioid 4,5-epoxymethylmorphinans, that are recognised to have therapeutic potential.[5] The other, the non-opioid isoquinolines, include the smooth muscle relaxant papaverine (**3**) and the antitussive noscapine.[6]



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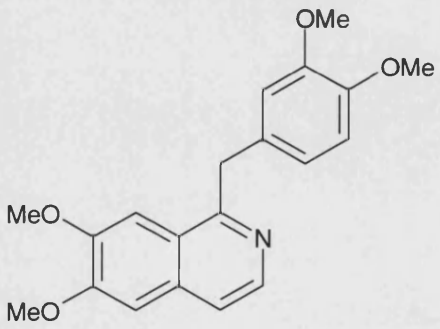

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1.2 Opioid receptors

1.2.1 The discovery of opioid receptors

The recognition of the common structural and stereochemical requirements of the narcotic opioids led to the hypothesis that there was a specific "opioid" receptor that mediated analgesia.[7] The evidence to validate this theory arrived in 1975 when Hughes and Kosterlitz successfully isolated two pentapeptides, leu-enkephalin and met-enkephalin[8,9], which were shown to have pharmacological properties very closely related to those of morphine. This breakthrough directly led to the conclusion that the pharmacological effects of the opioids were a result of their ability to mimic the binding of the endogenous peptides to specific receptors in the body. The enkephalins became the first in a class of peptides termed the "endogenous opioid peptides", characterised by the common tetrapeptide sequence Tyr-Gly-Gly-Phe.[10] Since then many more have been isolated, including the recently discovered nociceptin.[11]

1.2.2 Opioid receptor types

The theory that opioid receptors may exist as distinct types was first proposed by Portoghese[12] in 1965, but it was not until the work of Martin *et al.*[13] in 1976 that the first evidence to support this theory came to light. Martin proposed that the behavioural and neurophysiological effects of morphine, ketazocine and *N*-allylnormetazocine could be ascribed to three distinct receptor types: the μ (mu), κ (kappa) and σ (sigma) opioid receptors respectively. It was subsequently found that the effects mediated by the proposed σ receptor were not blocked by the universal opioid antagonist naloxone and were therefore non-opioid in nature.[14] The δ (delta) receptor was later proposed to account for the *in vitro* profile of the enkephalins[9] and it has now been firmly established that there are three major types of opioid receptor *i.e.* μ, δ and κ.

More recent research has provided significant evidence for subdivisions within each of these receptor types[15-17], though the existence of their distinct genes has not yet been proven; the possibility that these subdivisions may result from such phenomena as receptor dimerisation[18] cannot be ruled out. A fourth type of opioid receptor, the so-called orphan opioid receptor[11] (often termed ORL1), has also been identified and cloned but has yet to be fully characterised.

1.2.3 The structure of opioid receptors

Opioid receptors are part of the rhodopsin subfamily of G protein-coupled receptors characterised by the presence of seven transmembrane helices (Figure 1). The amino acid sequences of the opioid receptors are highly homologous (approximately 60% conserved identity), particularly in the transmembrane and intracellular domains.[10,19] They recognise a structurally diverse array of ligands which includes peptide sequences, natural products and synthetic small-molecule ligands.

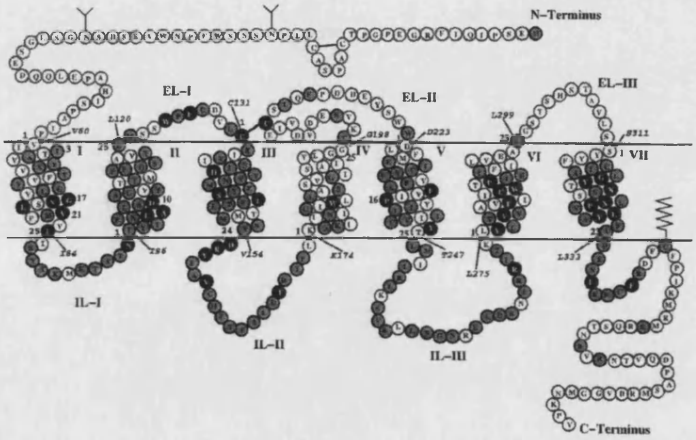


Figure 1 (Structure of the kappa opioid receptor[20])

1.2.4 Distribution and pharmacological profiles of μ, δ and κ opioid receptors

The distribution of opioid receptors was initially investigated by radioligand autoradiography[21] and later, with the development of cloning technology, by the detection of mRNA expression levels which correspond to cellular expression levels of the appropriate receptor type.[19,22] These studies have shown that all three receptors are widely distributed throughout the central nervous system, but μ and κ are also widely distributed on the wall of the gastrointestinal tract (particularly in the stomach and proximal colon). The δ receptor is also expressed on neurons within myenteric and submucous ganglia.[23]

As mentioned previously, the differing pharmacological effects of opioids are known to be mediated by the three types of receptor. The main pharmacological effects observed when bound by an agonist are summarised in Table 1. The table aptly demonstrates the striking range of actions produced by activation of opioid

receptors and is indicative of the great number of complex biochemical pathways invoked.

Mu (μ)	Delta (δ)	Kappa (κ)
Analgesia	Analgesia	Analgesia
Respiratory depression	Respiratory depression	Dysphoria
Euphoria	Convulsions	Sedation
Constipation	Constipation	
Physical dependance	Antidepressant	

Table 1 (Pharmacological effects resulting from activation of the three major receptor types)

1.3 The use of opioids in medicine and society

1.3.1 The mechanism of opioid analgesia

It is a fact known to almost everyone that opioids such as morphine and codeine are very powerful analgesics. Indeed, a glance at any medical formulary will reveal that, whilst a relatively wide range of opiates and synthetic opioid ligands are available to the prescriber, the vast majority are used solely for the purpose of pain management. Prescription of opioid drugs is normally reserved for conditions where other drugs, with less severe side-effects, have failed; however, they remain the treatment of choice to manage post-operative pain and chronic pain in cancer patients; in the latter case the side-effect of euphoria may even be regarded as beneficial.

Analgesia is induced when an agonist ligand binds to an opioid receptor. This causes the receptor to undergo conformational change which in turn initiates a series of events leading to dissociation of the G protein from the receptor and subsequent separation of the GTP bound G_α subunit from the $G_{\beta\gamma}$ dimer. Both the GTP bound G_α subunit and the $G_{\beta\gamma}$ dimer are then able to associate with effector molecules and modulate their biological functions.[4,24] Analgesia is mediated by all three opioid receptor types, although the vast majority of opioids used in medicine are somewhat selective towards the μ receptor. The three major mechanisms involved in opioid receptor-mediated analgesia are outlined below:

1. **Inhibition of adenylate cyclase by GTP bound G_α** – inhibition of adenylate cyclase reduces the production of cAMP which in turn effects reduction of voltage-dependent current and neurotransmitter release.[24]
2. **Inhibition of N-type Ca^{2+} channels by $G_{\beta\gamma}$** – inhibition of Ca^{2+} channels in the presynaptic neurone directly prevents the release of neurotransmitters into the synaptic cleft and hence inhibits signal transmission.[25]
3. **Activation of K^+ conductance** – activation of K^+ channels increases the outflow of K^+ from the neuron. This leads to postsynaptic hyperpolarisation and consequent inhibition of action potential propagation.[25]

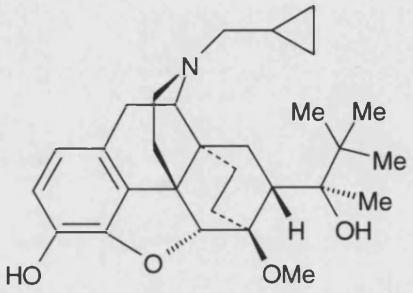
1.3.2 Other medicinal uses of opioids

Although medicine has tended to focus on the use of opioids in the management of pain, their wide pharmacological profile has been exploited in other, albeit less well-documented, applications. A brief survey of the major alternative current clinical applications of opioids is therefore appropriate.

Probably the most well-established and commonly prescribed opioid for treating conditions other than pain is codeine (**2**). Codeine's use as an antitussive (cough suppressant) has a long history and is a common ingredient in cough and cold remedies. The ability of morphine and codeine to produce constipation, normally an undesirable side-effect, is exploited as a treatment for diarrhoea although the peripherally-selective loperamide is normally preferred.[26]

Certain opioid receptor agonists also have an important role to play in the treatment of opioid addiction. Methadone remains the most common therapy and is a long-acting μ receptor agonist[4] which acts as a direct substitute for the opioid of abuse; research has shown that heroin addicts maintained on methadone are at a lower risk of death and are less involved in crime than when using heroin.[27] Methadone is itself an addictive substance, however, and so is not regarded as an ideal therapy. LAAM (levo-alpha acetyl methadol) was a widely used alternative to methadone which possessed the advantages of requiring only thrice weekly administration (thus improving compliance) and not producing a subjective high[28]; it has since been discontinued due to reports of adverse cardiac events. A rather different agonist frequently used to treat drug abuse is buprenorphine (**6**), which belongs to the oripavine class of thebaine derivatives.[29] Buprenorphine (**6**) is classified as a mixed agonist/antagonist, with partial agonist activity at the μ receptor

and antagonist activity at the κ receptor.[30,31] It has an exceptional safety profile, low physical dependence and minimal withdrawal symptoms[29,31,32], making it a highly attractive substance for combating opioid addiction.



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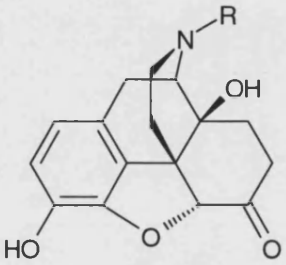

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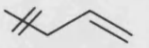

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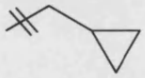


The use of opioid antagonists in medicine is currently relatively rare, although this situation is changing. Naloxone (**7**), synthesised in 1960, was the first antagonist to be widely exploited in medicine.[33] It effectively blocks all three receptor types and is used principally to reverse the effects of opioid overdosage[26], although it is occasionally present in compound preparations of opioid agonists to lessen the potential for dependence (Suboxone® is a combination of buprenorphine (**6**) and naloxone (**7**) used for the treatment of opioid addiction[34]). Of greater interest is the *N*-cyclopropylmethyl analogue naltrexone (**8**). Like naloxone, it has an affinity for all three types of opioid receptor but is somewhat μ selective.[4] At present, its major clinical application is in preventing relapse in addicts formerly physically dependent on opioids[26,35] which it achieves by blocking the euphoric effect associated with μ agonists. However, naltrexone has been shown to be successful in other types of addictive disorder including alcoholism[36], gambling[37] and hypersexuality[38] (co-administered with selective serotonin reuptake inhibitors).

Overall, there is considerable incentive for the development of new opioid agonists and antagonists, particularly those selective for a particular receptor and those with interesting pharmacological profiles.

1.3.3 Opioid tolerance and dependence

It cannot be denied that the powerful analgesic action of the opioids has alleviated the suffering of countless patients with chronic pain conditions to an extent which is unrivalled by any other class of drug. The prescribing of strong opioid analgesics is, as discussed in the previous section, normally reserved only for patients whose pain is not sufficiently relieved by other types of analgesic such as the non-steroidal anti-inflammatory drugs (NSAIDs). The relegation of opioids to a 'last resort' treatment is chiefly a result of the range of unpleasant side-effects that are induced on activation of opioid receptors (Table 1). Perhaps the most infamous unwanted effect of the opioids are their ability to produce tolerance and a state of dependence (often referred to as addiction) in chronic users. This is a serious issue in contemporary society and the main focus for this project (which is funded by the National Institute on Drug Abuse in the USA). A discussion of the current theories underlying the mechanisms of tolerance and dependence is therefore of relevence.

There is often much confusion over the meanings of the terms *tolerance*, *dependence* and *addiction* which refer to somewhat different phenomena. Tolerance is defined as the phenomenon in which an organism is less susceptible to the effect of the drug as a consequence of its prior administration. Dependence may be seen as a two-sided phenomenon consisting of a physical component and a psychological component:

- 'Physical dependence' refers to an altered physiological state whereby cessation of the drug or administration of an antagonist precipitates a withdrawal syndrome consisting of tremors, insomnia and a variety of other negative symptoms.
- 'Psychological dependence' is typified by a continued craving for the drug, manifested as compulsive, drug-seeking behaviour and an overwhelming involvement in drug procurement and use.
- 'Addiction' is less clearly defined and usually refers to a combination of physical and psychological dependence, with a particular emphasis on the latter.

1.3.4 The mechanism of tolerance and physical dependence

It was originally thought that the phenomena of opioid tolerance and dependence could be explained simply by an upregulation or downregulation of opioid receptors[39]; however, much evidence has since been accumulated which has shown this hypothesis to be incorrect. It is now generally accepted that opioid tolerance and physical dependence (psychological dependence is discussed in a later section) occurs as a result of multiple processes including G protein uncoupling, receptor endocytosis and changes at the post-receptor level.

Agonist activation of an opioid receptor leads to its phosphorylation by G protein coupled receptor kinases, which subsequently leads to binding of the receptor to regulatory proteins known as arrestins.[40] Arrestins are known to cause uncoupling of the receptor from its G protein and the striking work of Bohn *et al.*[41] confirms the importance of arrestins in mediating opioid tolerance: knockout mice lacking β-arrestin-2 failed to develop antinociceptive tolerance after chronic morphine treatment. Interestingly, the mice still developed physical dependence suggesting that the processes of tolerance and dependence are not as closely linked as was originally thought. An additional effect of the arrestins is to trigger the endocytosis of receptors. Such internalised receptors may then be dephosphorylated and recycled back to the plasma membrane in a fully active state, or targeted to lysosome for degradation.[40,42] It is now widely accepted that the endocytosis and subsequent recycling of receptors by β-arrestin contributes significantly to receptor resensitisation and the prevention of tolerance; thus arrestins appear to influence both desensitisation and resensitisation of opioid receptors.[40] Different opioid ligands have been shown to produce varying degrees of receptor recycling which have been expressed as RAVE (relative activity vs endocytosis) values.[42] Substances with low RAVE values, such as the endogenous opioid peptides, induce rapid endocytosis and recycling of receptors to their fully active state and hence resensitise the cell towards agonist. In contrast, substances with high RAVE values such as morphine, produce little endocytosis but persistently activate receptors; this leads to receptor uncoupling and the development of tolerance as discussed above.

Physical dependence is distinct from the phenomenon of tolerance and is thought to involve changes at the post-receptor level. By far the most extensively studied cellular mechanism in connection with physical dependence is the cAMP

pathway.[39,43] Figure 2 illustrates the change in intracellular cAMP and adenylate cyclase levels during chronic administration of morphine. Initiation of morphine produces an immediate inhibition of adenylate cyclase (and other signalling components) which in turn inhibits the cAMP pathway. On continued exposure, the level of adenylate cyclase and consequently cAMP recovers; cessation of morphine or administration of an antagonist results in sudden excessive cAMP production which is thought to be responsible for the withdrawal syndrome. The exact mechanisms leading to upregulation of adenylate cyclase and cAMP are at present unknown, though several lines of evidence indicate that cAMP-response-element-binding protein (CREB) may be involved.[39]

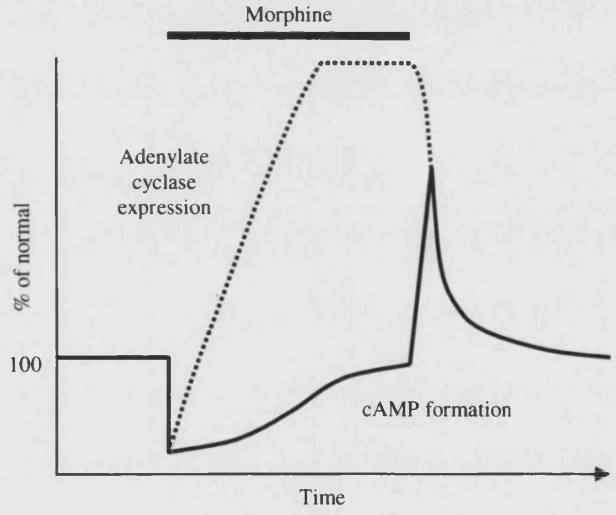


Figure 2 (Effect of chronic morphine administration on cAMP levels)

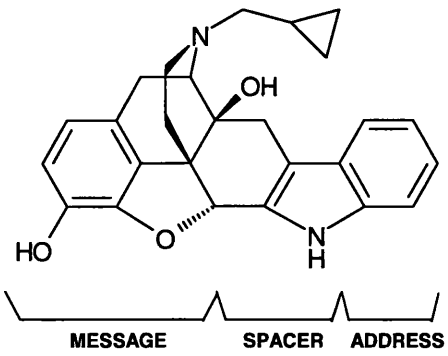
1.4 The development of selective opioid antagonists

It was discussed in the previous section that the use of opioid receptor antagonists in medicine is at present confined to a very small number of applications. Although new clinical uses for naltrexone (**8**) have been recently identified, the clinical (and research) use of opioid antagonists has to date been hampered by: a) the very limited range of clinically available compounds, and b) by the lack of available compounds that are greatly selective towards an individual receptor type.

1.4.1 The message-address concept and the development of naltrindole

A major turning point in the development of selective opioid antagonist ligands came when Portoghese successfully applied the "message-address" concept proposed by Schwyzer[44] in 1977 to the design of new selective opioid antagonist ligands. Schwyzer's original concept was based on analysis of the structure-activity relationships of peptide hormones, from which he proposed the existence of a "message" and "address" sequence of amino acid residues. The message component was postulated as influencing signal transduction at the receptor, whilst the address portion provided additional binding affinity to a particular receptor type but did not influence efficacy. This concept was applied to the endogenous opioid peptides by Chavkin *et al.*[45] who recognised a tetrapeptide message sequence (Tyr-Gly-Gly-Phe) and a variable address sequence which confers receptor selectivity.

The leap from peptidic agonists to non-peptidic antagonists was made by Portoghese and his colleagues in 1990, who envisaged that Schwyzer's model might be applicable to antagonist ligands derived from opioids such as naltrexone (**8**), if such ligands also interact with both the message and address subsites of the receptor. This proposal led to the design and synthesis of naltrindole[46] (**9**), a potent and δ selective antagonist. In this compound, the message component is a naltrexone-derived recognition unit joined to a benzene moiety which was thought to be the address component conferring δ selectivity in the enkephalins (later proved by modifying the structure of **9**). An additional feature not present in Schwyzer's original model is a spacer which acts to restrict the benzene ring to a single conformation, thought to increase selectivity by preventing conformational adaption to other receptor types.



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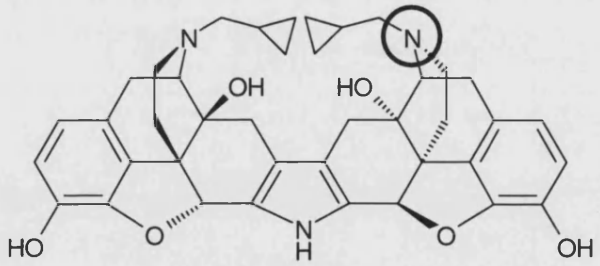
1.4.2 NorBNI and GNTI: Highly potent and selective kappa opioid antagonists

The message-address concept was to be later applied by Portoghese in what was effectively the reverse manner: rather than designing and synthesising a molecule combining a specified message and address moiety to give a selective antagonist as was the case for **9**, the model was instead used to *deduce* the address moiety for a particular receptor type based on knowledge of its selectivity.

During studies into the existence of dimeric opioid receptors, a series of naltrexone-derived bivalent ligands (*i.e.* containing two pharmacophores) with varying interpharmacophore spacers were synthesised.[10] It was found that greatest κ antagonist potency occurred when the two pharmacophores were linked solely by a pyrrole ring (norBNI, **10**).[47] This suggested that the potency increase was due to bridging of neighbouring recognition sites on a single receptor rather than bridging of a receptor dimer. The finding that the respective meso isomer was also κ selective[48] and somewhat more potent than **10** led to the conclusion that a *specific moiety* in the second pharmacophore of **10**, and not the pharmacophore itself, was responsible for κ selectivity. Superposition of the two structures revealed overlap of the N17' basic nitrogen (circled in **10**), suggesting it to be the key feature in defining κ selectivity. Subsequent experiments involving structural modification of **10** confirmed that a correctly positioned nitrogen was the only crucial requirement.[49]



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Thus it was concluded that the first pharmacophore of **10**, like **9**, binds to a "message" recognition subsite on the receptor, defining the molecule as an opioid receptor antagonist; meanwhile the second pharmacophore acts solely as a rigid scaffold to direct the protonated N17' moiety to an anionic κ recognition subsite.[10,49] Site-directed mutagenesis of the κ receptor revealed the address subsite to be the Glu297 residue, located at the top of transmembrane helix 6.[50,51] Increasing the

basicity of the address nitrogen by the positioning of a guanidine moiety on the 5' carbon atom of naltrindole (**9**) led to GNTI[51,52], the most selective κ antagonist ligand reported to date. Figure 3 illustrates the proposed binding mode of GNTI to the κ receptor, including the interaction of the "address" basic nitrogen with Glu297.

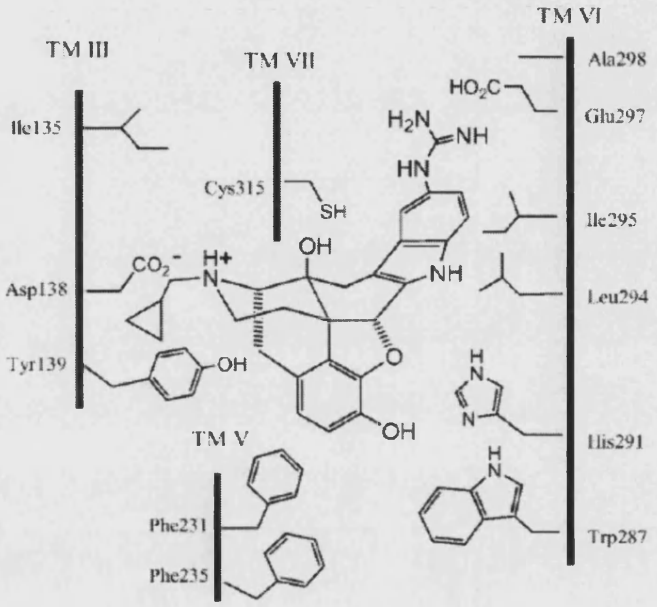


Figure 3 (Proposed model of interaction of **11** with the κ opioid receptor[24])

1.5 Kappa antagonists: A target for the treatment of addiction and depression

1.5.1 The mechanism of psychological dependence and the role of dynorphin

The phenomenon of psychological dependence is a major factor in the perpetuation of drug abuse but one which is currently poorly understood. It is now clear that psychological dependence is separable from physical dependence, as certain highly addictive drugs such as cocaine do not produce prominent physical dependence.[53]

Research into the area of psychological dependence has shown the problem to be a highly complex one, though certain brain regions and pathways have now been identified as playing important roles. Efforts have been particularly focused towards understanding the so-called brain-reward pathways, of which the mesolimbic dopamine system is now known to be the most significant.[53,54] In particular, the neurons linking the ventral tegmental area (VTA) to the nucleus accumbens (NAc) appear to be particularly important. The purpose of this primal pathway is to

produce a feeling of pleasure (by release of dopamine into the NAc) in response to certain stimuli such as eating or reproduction to ensure that the action is repeated in future.[54] Administration of nearly all drugs of abuse increase dopaminergic transmission in the NAc[53,55] (although some such as opioids can act directly on NAc neurons) thus activating the reward pathway and increasing the probability of administration recurring (*i.e.* positive reinforcement).

It was discussed in Section 1.3.4 that drugs of abuse such as morphine lead to an upregulation of the cAMP pathway and subsequent upregulation of CREB.[53,56] There is now evidence to show that upregulation of cAMP and CREB in the NAc may invoke a state of 'motivational tolerance and dependance' whereby the individual's sensitivity to the rewarding effects of the drug decrease with chronic exposure[53]; cessation of the drug then leaves the individual in an amotivational, depressed state. One of the contributing factors to this dysphoric mood is thought to be the CREB-mediated induction of the endogenous κ opioid peptide dynorphin. Dynorphin normally acts as a negative feedback mechanism to inhibit dopamine release in the NAc and thus control the reward pathway[57,58] (Figure 4). Upregulation of cAMP and CREB by chronic drug exposure leads to a concurrent upregulation of dynorphin.[53] During drug administration, the dysphoric effects of dynorphin (caused by its inhibition of dopamine) are countered by the euphoric effects of the drug; however, an abrupt withdrawal leaves a hyperdynorphic state resulting in depressed mood. This may be partly responsible for the "protracted abstinence syndrome" observed in individuals who have already undergone detoxification[59] where there is a high rate of relapse to drug abuse, possibly in order to escape the dysphoric mood state induced by dynorphin (*i.e.* negative reinforcement).

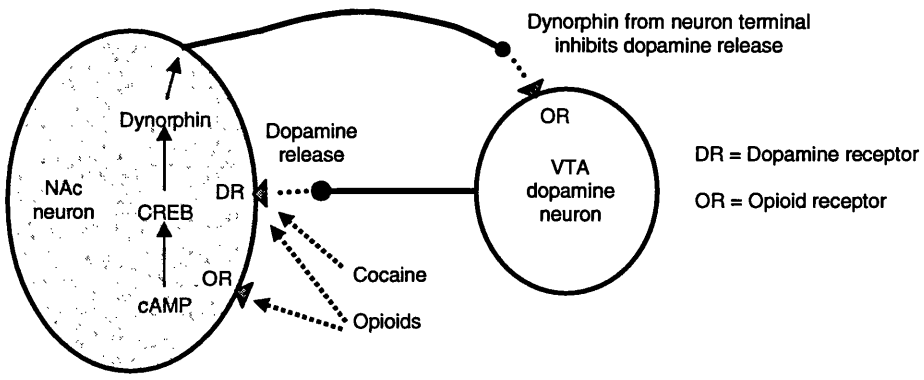


Figure 4 (Diagram illustrating the effect of dynorphin on the reward pathway)

New potential treatments for drug abuse are highly sought after as there are currently very few effective options available. The above findings have stimulated much interest in the potential clinical use of κ opioid antagonists in order to block the potent inhibition of dopamine in the NAc by dynorphin and consequently relieve the negative emotional symptoms of early drug withdrawal.[53,59]

The increased understanding of the effect of dynorphin on mood has driven concurrent studies to determine whether κ opioid antagonists would be effective in treating a wider variety of depressive states.[55,60,61] The neurobiology of depression is not well understood and the vast majority of drug treatments to date have targeted the serotonergic and noradrenergic systems. There is a current need for antidepressant medications that act faster (most current drugs take several weeks to produce beneficial effects) and have fewer unpleasant side-effects. To this end, research in the field is beginning to shift towards seeking alternative drug targets. Recent findings have shown that CREB-mediated transcription is induced in the NAc in response to acute and chronic stress.[55] Elevated expression of CREB has been found to increase immobility in the forced swim test[62], a common model used to study depression in rodents.[63] As discussed above, elevated CREB levels lead to an increase in dynorphin expression which could induce a dysphoric state *via* inhibition of dopamine release. Recent successful animal studies utilising the selective κ antagonist norBNI (**10**) have provided further support for the development of such compounds as antidepressants.[60,61]

Overall, there is much evidence to support the further study of selective κ antagonists in the treatment of drug abuse and depression. Although **10** has proved a highly useful research tool in animal studies, certain limitations to its use have since been identified and progress towards a clinically available κ antagonist for use in humans has been slow.

1.5.2 Limitations of current κ opioid antagonists

Selective receptor antagonists are highly important research tools in understanding the biochemical processes associated with specific receptors and in the accurate characterisation of receptor agonist ligands. The development of the highly selective κ antagonists norBNI (**10**) and GNTI (**11**) greatly accelerated understanding of the pharmacology of the κ receptor; however, *in vivo* studies conducted with these

ligands revealed certain unforeseen problems which now somewhat limits their use as research tools.

Although a highly effective ligand in terms of its potency and selectivity, there is now much evidence to show that **10** possesses an extremely long duration of action when administered both centrally and peripherally.[64] For example, a single dose of **10** was shown to potentiate κ antagonism for 49 days in rhesus monkeys.[65] Likewise, a study undertaken by Jewett and Woods in 1995 found that **10** continued to antagonise the κ agonist bremazocine even after 11 weeks.[66] Experiments performed with GNTI (**11**) have also shown it to possess a long duration of action: a study whereby rhesus monkeys were intramuscularly administered **11** showed that its effects were apparent for over 10 days in some cases.[67] These findings clearly indicate that **10** and **11** are unsatisfactory for many *in vivo* experiments as the period of time between successive administrations of the compound must be in the order of weeks and even then may still accumulate to potentially toxic levels in the test animal.

Since it has been shown that the effects of **10** are surmountable and therefore not a consequence of irreversible binding[66,68], another explanation must be sought to explain these observations. It was proposed by Takemori *et al.*[69] that the long duration of action of **10** may be partly a consequence of slow diffusion rates into and out of the brain, based on findings that its peak antagonist effect occurred an unusually long 2 hours after subcutaneous administration; however, since the effects of **10** persist long after the average turnover time of receptors, it is unlikely that this alone is responsible for the observed duration of action. One hypothesis proposed to explain these observations is that **10** may somehow be sequestered in the brain, but in such a way that it is still free to interact with κ receptors.[66] For this to occur, the diffusion processes into and out of the brain must not be equally effective for **10**, though the reason for this is not clear. It is interesting to note that **10** has been shown to have a high degree of non-specific binding in experiments with tritiated ligands[70], a possible contributing factor to its very long duration of action.

The evidence given above clearly imposes limitations on the use of **10** and **11** as both research tools and potential candidates for the clinical treatment of drug abuse and depression. There is thus a significant need to develop κ antagonist ligands with different pharmacokinetic profiles. The relative bulkiness of **10** and **11** (particularly **10**) is likely to impede their ability to cross membrane surfaces and has

been suggested to contribute to the slow onset of antagonist activity of norBNI (**10**).[69] It is also possible that this is a contributing factor to its extended duration of action. Therefore, by designing a molecule to include only those features which are necessary to obtain a selective κ opioid antagonist (with reference to the message-address concept), it should be possible to produce a set of ligands with superior diffusional properties which cross the blood-brain barrier more rapidly. The reduced bulk may also assist in overcoming whatever factor causes the activity of **10** and **11** to persist for so long and therefore produce a more favourable pharmacokinetic profile. Such a set of ligands would be of great use in research, both as tools for probing the κ receptor and in the development of pharmacotherapies for opioid abuse and depression. Several examples of such "small molecule" series of opioid receptor antagonists are present in the literature, though examination of the pharmacologies or syntheses of these compounds has revealed particular weaknesses with each.

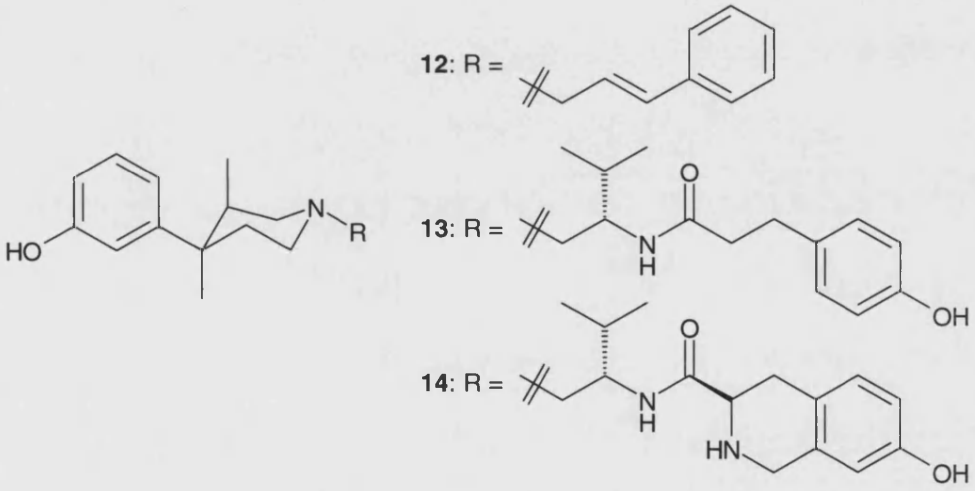
1.6 Literature survey of "small molecule" opioid receptor antagonists

The first (and most significant) series of opioid receptor antagonists to be reported which were not directly related to the epoxymorphinans (those compounds resembling morphine) were the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidines, disclosed by Zimmerman *et al.*[71] in 1978. In the epoxymorphinan series, the substituent of the bridging nitrogen appears to directly determine how the compound behaves at the μ opioid receptor. As a general rule, an *N*-methyl substituent affords μ agonist activity whereas *N*-allyl and *N*-cyclopropylmethyl groups result in antagonism of the μ receptor.[72] The *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine ligands were unique in that they all consistently behaved as pure antagonists at opioid receptors, even those possessing an *N*-substituent normally associated with agonist activity in the epoxymorphinans.[71] Thomas and his associates later expanded on the original series and disclosed the *N*-cinnamyl derivative **12** as a potent and selective μ antagonist.[73]

Inspired by the success of **12**, Thomas's group undertook the synthesis of a combinatorial library of compounds utilising the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidinyl scaffold, but avoiding those features that constituted the μ selective *N*-substituent of **12** in the hope of biasing selectivity toward the κ receptor.[74] Their efforts were rewarded when **13** was subsequently found to be a moderately potent and selective κ antagonist. Optimisation of the side-chain by

replacement of the phenol with a tetrahydroisoquinoline moiety subsequently afforded the far more potent and selective JDTic (**14**).[75] The increase in κ selectivity is thought to arise from interaction of the secondary amine group with the Glu297 residue of the κ receptor[76] in an analogous fashion to norBNI (**10**) and GNTI (**11**).

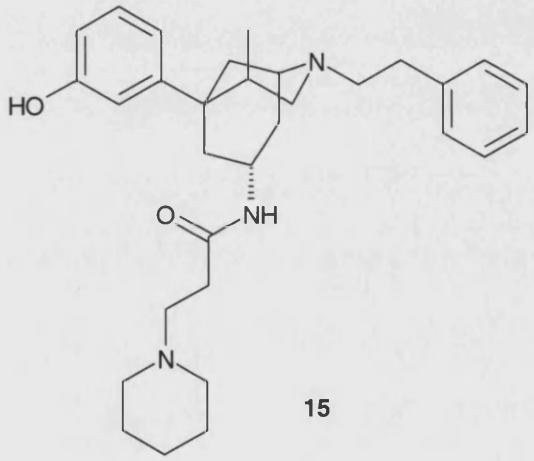
Of particular interest to the present project is that this series of compounds appears to obey the "message-address" concept discussed previously. The 'message' portion may be seen as the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidinyl scaffold, to which may be attached various 'address' substituents *via* the basic nitrogen in order to bias selectivity towards a particular receptor. Unfortunately, although **14** exhibited greater κ antagonist potency than norBNI (**10**), subsequent *in vivo* studies have found that it too possesses a very long duration of action in the order of weeks.[67,77]



Two other closely related series of compounds were later disclosed by Thomas, both of which afforded selective κ antagonists. The conformationally constrained *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan scaffold (directly derived from the 5-(3-hydroxyphenyl)morphans reported by Rogers and May[78]) was identified as a suitable opioid antagonist message to direct a piperidinyl side-chain address (**15**) towards the κ subsite.[79] The similarly constrained *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines were also found to yield antagonists[80], and substitution of the identical 3-(1-piperidinyl)propanamido address side-chain afforded similar potency at the κ receptor. However, a major drawback associated with both these series is their rather convoluted syntheses involving

certain steps which do not appear to lend themselves to larger-scale preparation *e.g.* the use of an organolithium reagent early on in both syntheses.

Small molecule opioid antagonists have also been obtained by the simple structural alteration of existing agonist ligands. The irreversible κ-selective compounds UPHIT (**16**) and DIPPA form the most significant antagonists to arise from the structurally distinct arylacetamide class. **16** was derived directly from the highly selective κ agonist U50488[81,82] (frequently used in opioid binding assays) and differs only in the presence of an aromatic isothiocyanate group which binds covalently to the receptor leading to irreversible blockade. It appears unlikely though that this series will afford reversible opioid antagonists.



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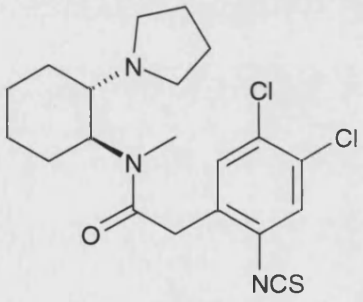

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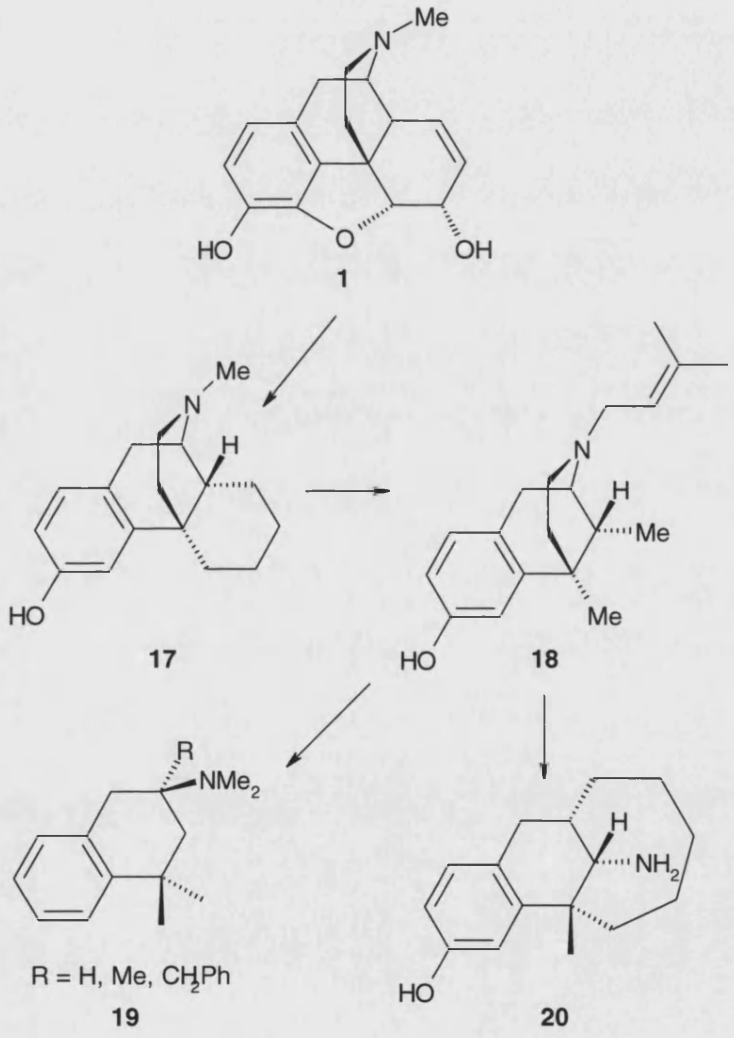
1.7 Aminotetralins: Novel 'message' scaffolds for the development of selective opioid receptor antagonists

As a first step in the search for a new scaffold on which to construct novel small-molecule opioid receptor antagonists, it was decided to examine how simplification of the morphine skeleton had previously led to series of active opioid ligands. Scheme 1 illustrates how fragmentation studies and efforts directed towards the total synthesis of morphine led to the identification of analgesics often many times more potent than morphine but with progressively simpler structures. Levorphanol (**17**) belongs to the morphinan family which notably lack the characteristic furan bridge of the opiates and can be considered to be the first stage in the simplification of morphine.[24] Exclusion of the D-ring of the morphinans subsequently led to the benzomorphans of which the clinical analgesic pentazocine

(**18**) is the most interesting, possessing a degree of κ selectivity.[4] Further alteration of the benzomorphan structure led to the phenylpiperidines, from which JDTic (**14**) and the other Thomas compounds are derived. The drawbacks of this series discussed previously led to consideration of how else the benzomorphan structure might be simplified to provide ligands with differing pharmacological profiles and increased synthetic accessibility.



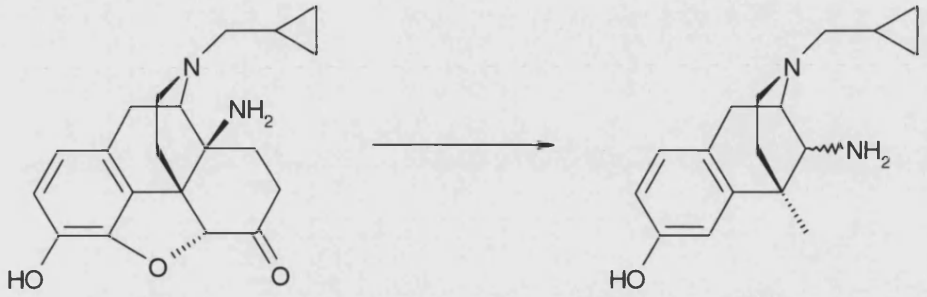
Scheme 1 (Structural simplification of the morphinans)

Further survey of the literature brought attention to the aminotetralins, of which several previous studies have identified activity at opioid receptors. Martin *et al.*[83] reported series **19** in 1969 which possessed potencies weaker than morphine but were remarkable in their structural simplicity. Later structural modification incorporating a bridging ring afforded dezocine (**20**)[84], with an agonist potency similar to that of morphine. Interestingly, **20** was found to precipitate withdrawal symptoms in morphine-dependent monkeys[85], indicating that the compound is in fact a partial agonist. The aminotetralins therefore appeared attractive starting points for the development of short-acting selective opioid ligands: studies of **19** and **20** proved they had significant affinity for opioid receptors; in addition they are small, structurally simple molecules which may translate to a favourable *in vivo* pharmacokinetic profile.

Given that the studies of **19** and **20** as opioid ligands reported significant agonist activity, one issue of primary importance to this project was whether it would be possible to derive pure antagonist ligands from an aminotetralin scaffold. It has been shown that substituting side-chains (particularly those possessing a three carbon chain and terminal aryl group) at the 14β-amino moiety of morphinone **21** consistently results in potent opioid receptor antagonists.[86] Using molecular modelling, a structural similarity between the 14β-amino group of **21**, the basic nitrogen of the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine series (**12-14**) and the primary amine group of **20** was clearly recognisable. This suggests that 2-aminotetralins such as **20** may yield selective antagonist ligands in the same way as **12-14** if the primary amine function is furnished with a suitable 'address' side-chain. It is worthwhile to note that the original paper where **20** is disclosed also reports the synthesis of analogues possessing simple *N*-methyl and *N*-dimethyl side-chains.[84] These were found to have a significantly lower analgesic potency than the unsubstituted parent compound **20** and were consequently abandoned; however, only agonist activity was measured in this study and any antagonist properties these compounds may possess remain unknown.

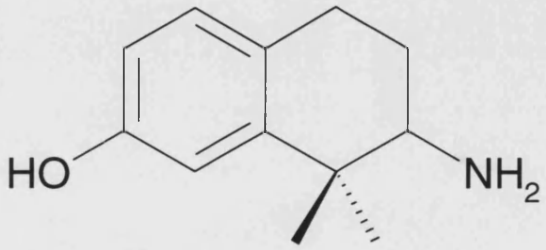
Benzomorphan **22** was initially considered as a potential scaffold: bearing such strong structural resemblance to **21**, it would be expected to retain antagonist activity. Structure-activity relationships of benzomorphans based on **18** showed the *N*-cyclopropylmethyl group to confer potent opioid antagonist properties[87], providing additional support for **22** as a suitable scaffold. However, examination of the

literature revealed the large majority of benzomorphan syntheses to be somewhat convoluted and low yields were frequently encountered in formation of the bridging ring.[88-90]



21 **22**

Studies of the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine series amongst others have clearly shown that it is possible to produce antagonist ligands which do not possess a bridged system and the associated synthetic complications seem a very reasonable basis for us to exclude such a bridge from our scaffold. Furthermore, if our modelling studies are correct and the primary amine moiety of the 2-aminotetralins directly mimics the basic nitrogen of **12-14**, then an additional tertiary amine group on an adjacent carbon is not necessarily required for antagonist activity. Evidence to support this conjecture is provided by the reported mixed agonist-antagonist properties of **20** and by Reifenrath and Fries[91] who report an *N*-cyclopropylmethyl 2-aminotetralin as being a weak opioid antagonist. After thorough consideration of these issues, it was decided that aminotetralin **23** may have the potential to act as a scaffold on which to construct selective opioid antagonist ligands.



23

The structure of **23** was envisaged as satisfying the primary criteria for the design of the new scaffold, namely synthetic accessibility and structural simplicity, whilst retaining features which should give rise to opioid receptor binding. Additionally, **23** bears sufficient structural distinction from the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine scaffold that it may afford ligands with differing pharmacokinetic profiles. Aminotetralin **23** may be seen as possessing three key structural features, each of which was included to enhance opioid receptor binding and consequently the ability of **23** to act as a suitable opioid 'message' scaffold:

1. The phenolic group is a very common structural motif of opioid ligands and structure-activity relationships have established that the presence of a phenol in the 3-position, as is the case for naltrexone, is optimum for binding to opioid receptors.[72,92] Mimicry of the tyrosine residue common to the endogenous opioid peptides may explain this observation.
2. A geminal dimethyl group is incorporated to mimic part of the bridging ring found in the epoxymorphinan and benzomorphan series. Such a quaternary centre was incorporated into the series of aminotetralins synthesised by Martin *et al.*[83] and is thought to enhance binding.
3. The primary amine moiety is intended (as discussed above) to mimic the basic nitrogen of the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine scaffold and provide the means to attach various 'address' side-chains to bias selectivity towards a particular receptor. A correctly positioned amine group is in any case known to be essential for opioid receptor binding – electrostatic interaction with an anionic aspartic acid residue is probably the primary cause[24,72] (see Figure 3).

In order to further investigate the relationship between **23** and the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine scaffold of ligands **12-14**, the two structures were overlayed using the molecular modelling program MOE[93]. Figure 5 shows the result obtained when the respective phenolic moeities of the two structures are aligned. The spacial overlap of the amine protons of the two basic nitrogen centres

(arrow **A** in the figure) is particularly encouraging, as this suggests that the amine moiety of **23** should interact with the same amino acid residues in the receptor as the basic nitrogen of the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine scaffold; hence a similar spectrum of antagonist activity may be obtained with **23** by the substitution of suitable 'address' side-chains.

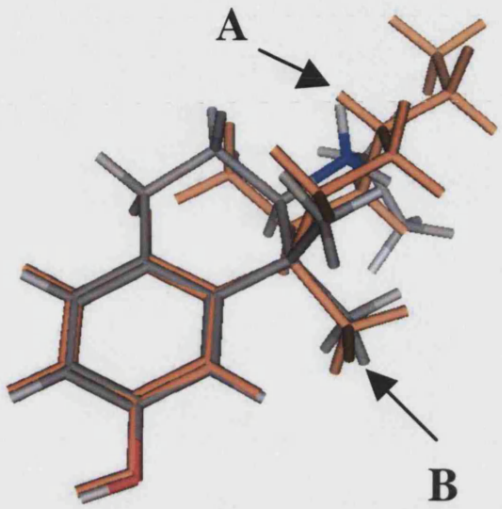


Figure 5 – (Overlap of aminotetralin **23** [grey] and hydroxyphenylpiperidine scaffold [orange])

The other noticeable feature of Figure 5 is the proximity of the axial 4-methyl group of the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine scaffold to one of the *gem*-methyl groups of **23**. Carroll *et al.*[80] have previously elucidated that the 4-methyl group is important for the activity of this series at opioid receptors; the observed spacial overlap suggests that the *gem*-dimethyl group of **23** may mediate a similar effect in the present series of ligands.

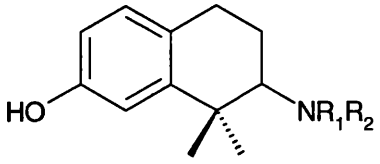
Overall, there is clearly much scope for the investigation of aminotetralin **23** as a potential scaffold for the development of selective, short-acting opioid receptor ligands.

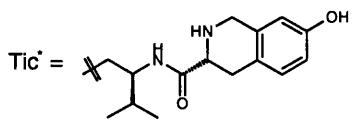
1.8 Investigation of 2-amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol as a new opioid receptor 'message'

A series of preliminary compounds utilising the novel aminotetralin scaffold **23** were recently synthesised and biologically evaluated within the group. In each case, the primary amine moiety of **23** was either mono- or di-substituted with a

simple hydrocarbon side-chain (methyl, propyl, allyl, cyclopropylmethyl or cinnamyl), using a combination of either direct alkylation with the appropriate halide or reductive alkylation with the aldehyde. The side-chains were not specifically designed to confer selectivity towards a particular receptor type, rather to preliminarily evaluate the effectiveness of **23** (if any) as an opioid receptor antagonist scaffold. Intrigued as to whether a selective κ antagonist could be obtained by combining the isopropyl-tetrahydroisoquinoline side-chain of JDTic (**14**) with scaffold **23**, it was decided that the corresponding aminotetralin analogue would also be synthesised. Compounds were submitted for binding and functional assays as their hydrochloride salts. K_i values for opioid binding were determined by displacement of standard tritiated agonist ligands from cloned human opioid receptors transfected into chinese hamster ovary cells.[94] Functional antagonist activity (expressed as K_e) was measured by *in-vitro* inhibition of [^{35}S]GTPγS binding to cells transfected with cloned human opioid receptors.[94] The full experimental details are given in Chapter 7.

The majority of the compounds showed little potency or selectivity for any of the three types of opioid receptor in either the binding or functional assays, though with some notable exceptions. Tables 2 and 3 summarise the results of the binding and functional assays for selected compounds of this series.





			K_i ± SEM (nM)		
No	**R_1**	**R_2**	**μ [^{3}H] DAMGO**	**δ [^{3}H]Cl-DPDPE**	**κ [^{3}H]U69,593**
24	^{n}Pr	Me	85.0 ± 14.7	2090 ± 22.8	184 ± 29.4
25	Allyl	Allyl	105 ± 0.89	672 ± 127	55.8 ± 18.6
26	Cinnamyl	H	10.7 ± 2.73	472 ± 108	82.3 ± 18.0
27	Tic*	H	23.0 ± 2.75	139 ± 52.1	5.04 ± 0.60

Table 2 (Binding assay results for selected compounds derived from scaffold **23**)

			$K_e \pm$ SEM (nM)		
No	**R_1**	**R_2**	**vs DAMGO μ**	**vs Cl-DPDPE δ**	**vs U69,593 κ**
26	Cinnamyl	H	67.7 ± 7.59	Not tested	42.7 ± 2.75
27	Tic*	H	139 ± 31.7	503 ± 120	3.04 ± 0.18

Table 3 (Functional assay results for selected compounds derived from scaffold **23**)

Compound **26** bearing an *N*-cinnamyl substituent was revealed as the most interesting of the simple hydrocarbon series, possessing relatively high affinity for μ receptors and moderate affinity for κ receptors. Although **26** is not as potent or μ selective as the corresponding *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine analogue **12**, the result clearly demonstrates that ligands derived from scaffold **23** have significant affinity for opioid receptors and appear to behave exclusively as antagonists. An equally significant result was the finding that JDTic analogue **27** is a potent and selective antagonist for the κ receptor. The binding and functional assay results are comparable to **14**, although **27** was again less potent than the corresponding *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine analogue.

The above results quite clearly illustrate that **23** is indeed a suitable scaffold for the construction of opioid receptor antagonists. The strong correlation of structure-activity relationships between this series and the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine compounds indicate that the two basic nitrogen centres are equivalent and consequently ligands derived from **23** also obey the 'message-address' concept. Although **26** and **27** were less potent than the corresponding compounds reported by Thomas *et al.*, the structure of **23** is unoptimised for opioid receptor binding and consequently there is much scope for improvement to this scaffold.

1.9 Research aims

The aim of this project is to expand on the previous work carried out in our research group using the novel aminotetralin scaffold **23**, in order to further progress towards a series of short-acting selective κ opioid antagonists for use as research tools and treatments for drug abuse and depression. The specific aims of the project are:-

- To synthesise further ligands derived from scaffold **23** possessing novel side-chains designed to increase selectivity for the κ opioid receptor over the μ and δ receptors.
- To investigate structural modifications to scaffold **23** to increase the affinity of the 'message' portion of the ligand for opioid receptors - this should result in ligands of increased antagonist potency.
- To examine and improve the existing synthetic routes to aminotetralin **23** and the new ligands described above, with the aim of developing procedures suitable for larger scale preparation of intermediates. A particular emphasis will be placed on the development of routes using inexpensive, non-toxic and easy-to-handle reagents where possible.

CHAPTER 2

RING-SUBSTITUTED *N*-CINNAMYL DERIVATIVES OF 2-AMINO-1,1-DIMETHYLTETRAHYDRONAPHTHALEN-7-OL

2.1 Design rationale

The preliminary investigations into the suitability of aminotetralin **23** as a scaffold on which to build opioid antagonist ligands revealed *N*-cinnamyl derivative **26** as possessing significant affinity for the μ and κ receptor types. This was an encouraging result as it directly indicated that selective, small-molecule opioid antagonists may be derived from such a system. A high degree of selectivity for one receptor type is desirable for a ligand to be of value as a research tool and since **26** does not possess any significant μ vs κ selectivity, it was decided to consider whether simple structural modifications to **26** might lead to a more favourable pharmacological profile whilst retaining synthetic accessibility. As the present project is particularly focused on the synthesis of κ-selective antagonists, it appeared that application of the 'message-address' concept to the development of such ligands may be of particular value.

It was discussed in the previous chapter that the presence of a correctly positioned basic nitrogen moiety is thought to be the determining factor in the κ selectivity of compounds such as norBNI (**10**) and JDTic (**14**). A rigid scaffold acts as a spacer between the 'message' pharmacophore and directs the protonated amine 'address' group into a position where it is able to form an ionic interaction with the Glu297 residue of the κ subsite. It appeared that by attaching a guanidine or similar functionality to the terminal phenyl group of **26**, a basic group could be orientated into an equivalent position where such an interaction with Glu297 could be established.

The double bond of the propenyl spacer and the phenyl group of **26** impart a degree of structural rigidity to the system; such conformational restriction can be advantageous in enhancing receptor selectivity and affinity as it lowers both the potential for interaction with other receptors (thereby increasing selectivity) and decreases the adverse entropy change on binding[95] (increasing the free energy of binding and hence affinity). It was therefore decided to retain both of these features. In addition to providing structural rigidity to the spacer, the aromatic ring also allows

for three differing positions of the crucial basic group. Figure 6 shows the overlay diagram obtained by aligning the phenolic moieties of GNTI (**11**, orange) and the cinnamyl derivative of the new aminotetralin scaffold (**26**, grey); the proximity of the basic guanidine moiety of **11** to the *ortho*, *meta* and *para* positions on the terminal aromatic ring of **26** are indicated by arrows. Thus the ability to vary the position of the basic group in this manner increases the likelihood of obtaining the desired κ selectivity.

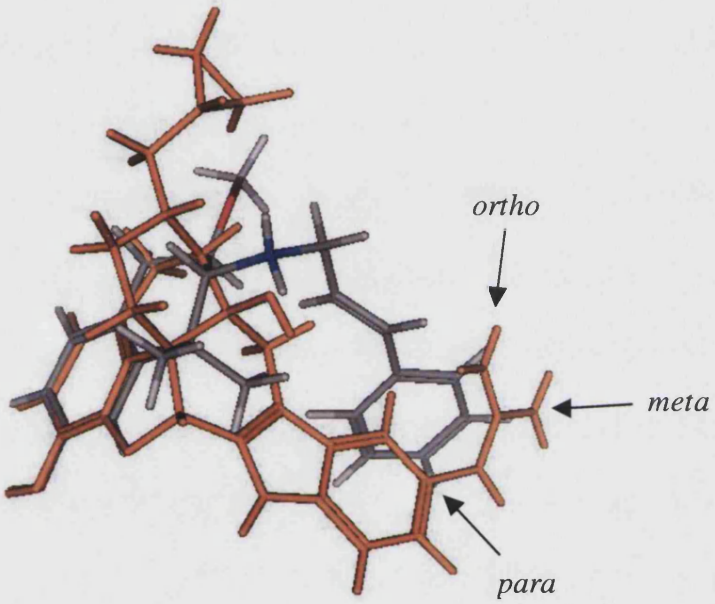
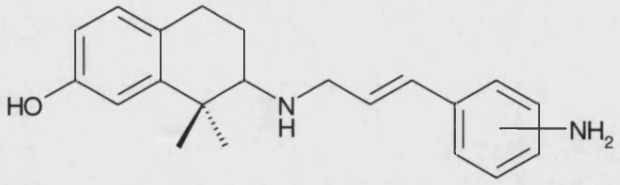


Figure 6 (Overlay illustrating the proximity of the guanidine group of **11** to the *o*, *m* and *p* positions on the terminal aromatic ring of **26**)

Whilst guanidine-substituted analogues of **26** were the eventual intended targets of this project due to the high basicity of this functional group, it was decided to initially focus on the synthesis of the intermediate primary amines **28-30** from which the corresponding guanidine ligands would later be prepared. In addition to being synthetically more accessible than the guanidines, the pharmacological evaluation of **28-30** would increase the very limited structure-activity information on this series and may provide an insight into which position on the terminal aromatic ring the basic group should be placed to afford greatest κ receptor selectivity.

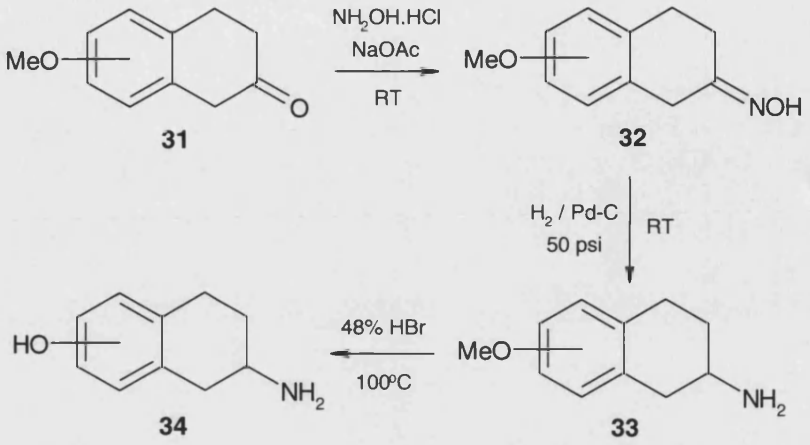


28: ortho
29: meta
30: para

The work of Portoghese showed that κ selectivity correlated directly with the basicity of the 'address' nitrogen – the guanidine derivative GNTI (**11**) possessing the greatest selectivity of all.[10,52] On this basis, the primary amine group of **28-30** (pK_a of aniline = 4.63) would not be expected to exhibit particularly high κ selectivity compared to the guanidine analogues (pKa of guanidine = 12.5) due to delocalisation of the nitrogen's lone pair of electrons around the aromatic ring. Conversely, it may also be argued that a guanidine group could enhance interaction of the ligand with the receptor to a point where the pharmacokinetic profile becomes undesirable and the ligand possesses a long duration of action *in vivo* (as reported for **11** – see Section 1.5.2). It therefore appeared logical to begin with an 'address' amine of relatively low basicity (*i.e.* the primary amine in **28-30**); if the degree of κ selectivity is found to significantly increase relative to **26** then the investigation of other amine 'address' moieties of intermediate basicity (*i.e.* pK_a 5-12) may be justified before progressing to the highly basic guanidines.

2.2 Literature methods of 2-aminotetralin synthesis

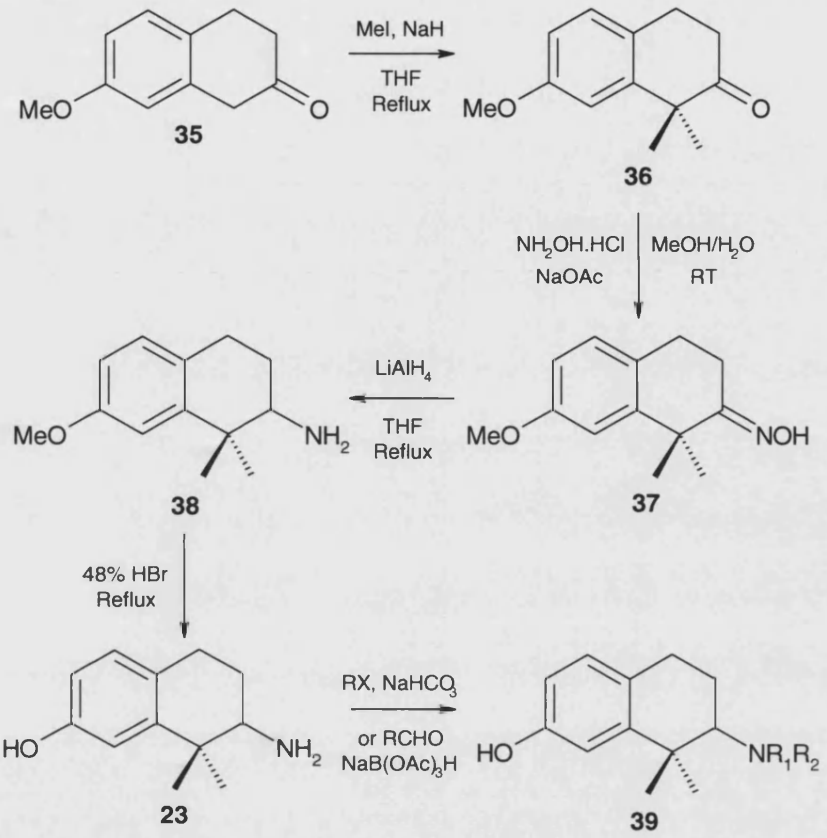
The synthesis of basic 2-aminotetralin skeletons is well established in the literature and numerous examples have been previously reported as the starting points for ligands acting at opioid, dopamine and adrenergic receptors amongst others. The actual synthetic route employed does not in general vary significantly between literature reports, and the pathway followed by Ye *et al.*[96] is typical (Scheme 3). In this example, the commercially available 2-tetralone (tetrahydronapthalenone) **31** is first converted to its corresponding oxime **32** by standard reaction with hydroxylamine hydrochloride under mildly basic conditions. The oxime is subsequently reduced by catalytic hydrogenation to afford primary amine **33**, which is then subjected to 48% aqueous hydrobromic acid at 100°C to afford 2-aminotetralin **34**.



Scheme 3 (Typical literature synthesis of 2-aminotetralins[96])

A particular advantage of using the route illustrated in Scheme 3 as the basis for the synthesis of aminotetralin **23** is that the ketone moiety of the starting material **31** considerably enhances the acidity of protons at the 1-position due to conjugation of the resulting enolate. Thus deprotonation of **31** with a relatively strong base and subsequent alkylation with halide would appear to be a favourable method for the introduction of the geminal dimethyl group of **23** into the structure; the ketone may then be converted to the oxime as before, followed by subsequent reduction and *O*-demethylation. Indeed, this was the route previously adopted within the group for the synthesis of scaffold **23** (Scheme 4). The actual transformations remained virtually identical to those of Scheme 3, though the oxime reduction was performed using refluxing lithium aluminium hydride as this was considered to be more convenient than high pressure catalytic hydrogenation.

One significant drawback of this route is the relatively high price (~£30/g) of the starting material, 7-methoxy-2-tetralone (**35**). In addition, the compound is somewhat unstable (3,4-dehydrogenation to the thermodynamically favourable conjugated ketone being the most likely pathway) and must be stored at subzero temperatures.

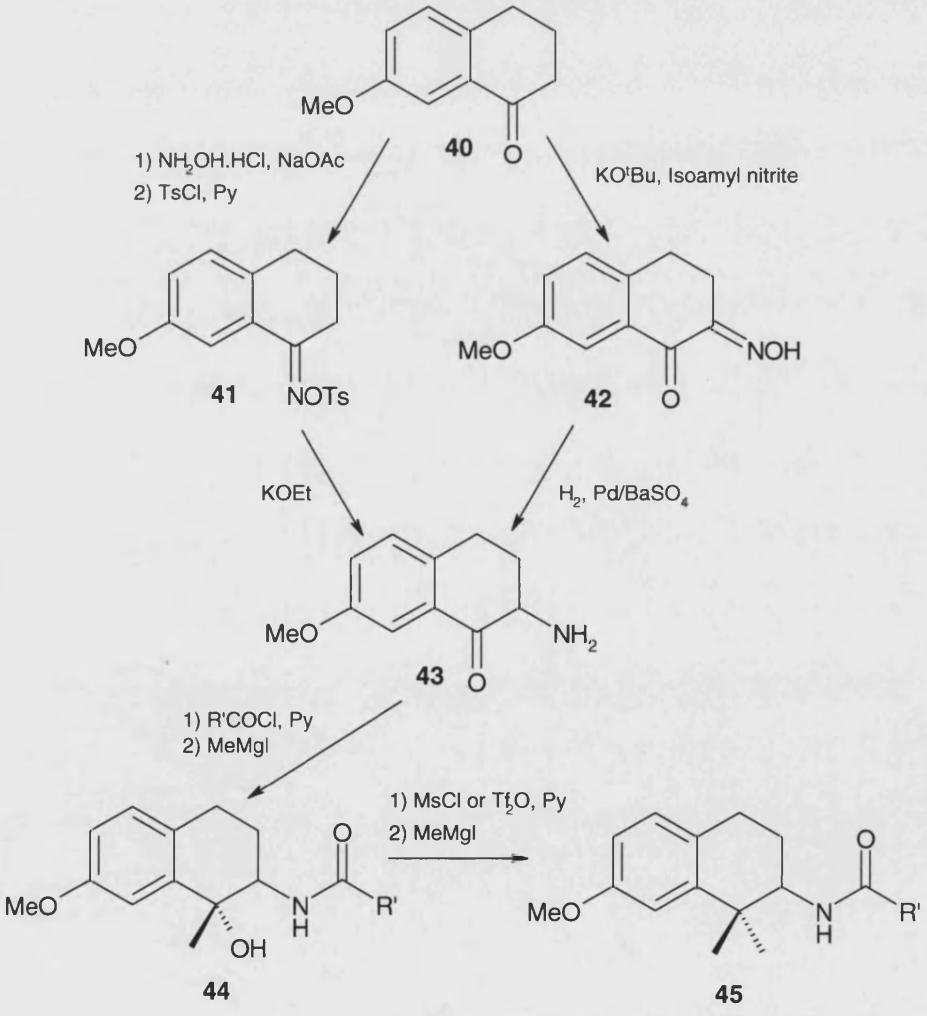


Scheme 4 (Route previously employed for synthesis of **23** and derivatives)

There are very few reports in the literature of 1,1-disubstituted 2-aminotetralin syntheses; however, a rather different approach based on the route applied by Reifenrath *et al.*[91] begins with the significantly less expensive 7-methoxy-1-tetralone (**40**) (Scheme 5). The key intermediate is α-ketoamine **43**, which may be formed by nitrosation of **40** with potassium *tert*-butoxide and isoamyl nitrite to yield the oxime **42** after tautomerisation, followed by selective catalytic hydrogenation. An alternative synthesis of **43** would be formation of the *O*-tosyloxime **41**, followed by Neber rearrangement with potassium ethoxide). Intermediate **43** is then rapidly acylated with the desired side-chain (which prevents self-polymerisation), leaving the ketone group free to undergo addition with Grignard reagents. In the series of Reifenrath *et al.*[91] 1,1-disubstitution was introduced by addition of phenylmagnesium bromide, followed by alkylation of the resulting tertiary alcohol to form ethers. To introduce a geminal dimethyl group, the most direct approach from **43** would appear to be addition of methylmagnesium iodide to afford **44**. Conversion of the alcohol

moiety to a more labile methanesulfonate or triflate group, followed by further reaction with methylmagnesium iodide should yield the 1,1-dimethylated **45**. Reduction of the amide group and subsequent *O*-demethylation would then afford the desired ligands.

Although the alternative route to 2-aminotetralins (Scheme 5) may prove to be somewhat more economical than the previously employed route (Scheme 4), it was decided after consideration to concentrate on the optimisation of the prior route; one particular advantage being that diversification occurs at a much later stage in the synthesis, allowing analogues to be prepared with greater efficiency.



Scheme 5 (Alternative approach to 1,1-disubstituted 2-aminotetralins)

In view of the high price of the starting ketone (**35**), it appeared appropriate to examine whether laboratory synthesis from less expensive materials might be feasible. Examination of the literature revealed that **35** may indeed be prepared in a two step route from 2,7-dihydroxynaphthalene, a commercially available and inexpensive material (~£0.20/g).

2.3 Synthetic studies

It quickly became apparent after the preliminary *in vitro* results that large quantities of aminotetralin **23** (and the intermediate oxime **37** which is the starting point of a later synthesis) would be required and consequently much time was invested into improving and optimising the experimental procedures. Additionally, the availability of multigram quantities of **23** would increase the feasibility of optical isomer separation by fractional crystallisation - this would allow the active isomer of pharmacologically significant ligands to be identified.

2.3.1 Synthesis of 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-one

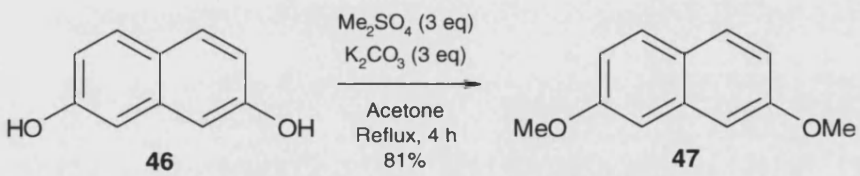
Investigation of the laboratory preparation of tetralone **35** was considered important due to the vast difference in cost compared with its precursor, 2,7-dihydroxynaphthalene (**46**). The two-step synthesis begins with the dimethylation of **46** to afford diether **47**. The reaction was initially attempted by deprotonation of diol **46** with the aggressive base sodium hydride in DMF in order to promote complete conversion to its dipotassium salt. Iodomethane was employed as the alkylating agent and an 87% yield of pure 2,7-dimethoxynaphthalene (**47**) was obtained after quenching and filtering. It quickly became apparent, however, that this method was not suitable for preparing larger quantities of **47** due to the hazardous nature of sodium hydride.

The weaker but considerably less hazardous base potassium carbonate is commonly used for the formation of ethers from phenolic compounds[97] and appeared an attractive alternative to sodium hydride for large scale preparations. A solution of **46** was therefore treated with 3 equivalents of potassium carbonate and iodomethane, the resulting mixture being heated to reflux overnight. Although acetone is the standard solvent for such reactions, ethanol is occasionally used[98] but in this case resulted in a lower yield of **47** (see Table 4); a significant quantity of unreacted starting diol remained in both cases and it was thought that this could be partly due to

iodomethane escaping from the system (bpt. of iodomethane is only 42°C). When iodomethane was replaced with dimethyl sulfate (bpt. 188°C), consistently high yields (>80%) were obtained after only 4 hours at reflux (Scheme 6).

Electrophile/Base	Solvent	Conditions	Yield
MeI / NaH	DMF	RT, 18 hrs	87%
MeI / K_2CO_3	EtOH	Reflux, 18 hrs	62%
MeI / K_2CO_3	Acetone	Reflux, 18 hrs	70%
Me_2SO_4 / K_2CO_3	Acetone	Reflux, 4 hrs	81%

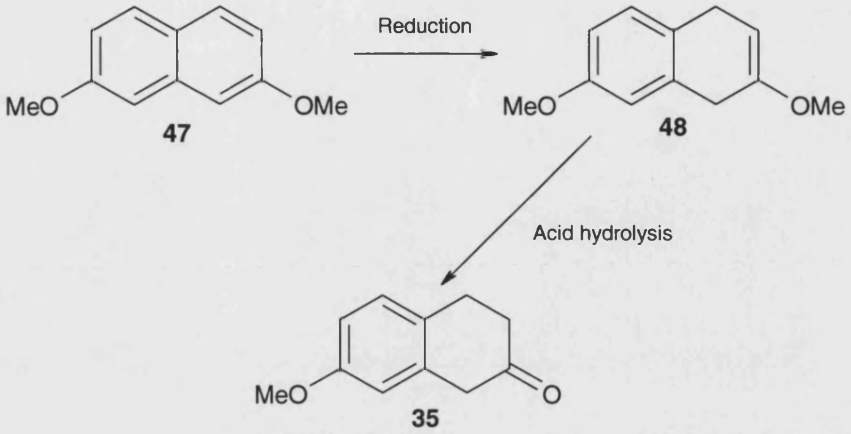
Table 4 (Reaction conditions used to attempt dimethylation of **46**)



Scheme 6 (Optimum dimethylation method of **46**)

An alternative improved work-up procedure which avoids partitioning and extraction of the crude product was also devised. Previously, the product **47** had been obtained in the 'classical' manner by partitioning the reaction mixture between diethyl ether and aqueous sodium hydroxide solution followed by sequential extractions with diethyl ether. Further investigation found that by simply adding a 4M aqueous solution of potassium hydroxide to the cooled reaction mixture (which dissolves both unreacted **46** and potassium carbonate) followed by evaporation of the acetone *in vacuo*, the pure ether **47** precipitates and can be easily collected by suction filtration, dried and used without further purification in the next step.

Transformation of diether **47** to tetralone **35** may be considered to be a two step process, involving reduction of **47** to the 2,3-enol ether **48** which is subsequently hydrolysed to afford ketone **35** (Scheme 7); isolation of the intermediate **48** is not undertaken, however, and the process may be conveniently conducted in one pot.



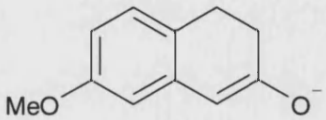
Scheme 7 (Conversion of diether **47** to tetralone **35**)

Consultation of the literature shows that reduction of **47** to **48** has been achieved using two mechanistically identical but experimentally distinct approaches. The Birch reduction, involving the transfer of single electrons from alkali metals to substrates, is a widely applicable technique for the reduction of aromatic rings[97] and reliably results in a characteristic 1,4-dihydro pattern of reduction. The classical conditions of the Birch reaction involve introducing a solution of the substrate in an alcohol (commonly ethanol) to a deep blue solution of the alkali metal (typically sodium) in liquid ammonia at –78°C. Application of this technique to diether **47** constitutes one of the two main approaches to **48**, and tetralone **35** may be readily obtained after acid hydrolysis.[99]

A somewhat different technique to effect reduction of mono- and dimethoxynaphthalenes was developed earlier by Cornforth *et al.*[100] in 1942. This method also uses sodium metal as a source of electrons and may be considered as mechanistically identical to the Birch reduction. The two techniques diverge, however, in their choice of reaction solvent and conditions. Unlike the Birch reduction, the procedure of Cornforth stipulates refluxing ethanol as the solvent of choice. Although the quoted yields are generally inferior to those of the Na/NH_3 Birch reduction, the practical disadvantages of liquid ammonia make the Cornforth method more convenient for repeated large scale preparations of **35**. With this in mind, it was decided to pursue the Cornforth method of reduction and investigate whether alterations to the literature procedures could be made to increase the yield of tetralone.

The process of reducing **47** to enol ether **48** was initially carried out in essentially the same manner as described by Cornforth for 2-methoxynaphthalene. This involves adding an excess (approximately 10 equivalents) of freshly cut sodium metal in small pieces to a refluxing solution of **47** in ethanol. Higher yields of **35** were generally obtained when the addition of sodium was carried out as quickly as possible. Commencing the addition below reflux temperature resulted in a considerably diminished yield of tetralone, with no reaction occurring at all at room temperature.

The resulting enol ether **48** was subsequently hydrolysed to the tetralone by the rapid addition of 5M hydrochloric acid at 0°C (which also serves to protonate the sodium ethoxide formed). A deep blue colour is observed during the addition, referred to as 'tetralone blue' in the literature[100]. Presumably, this colouration originates from deprotonation of **35** by residual sodium ethoxide forming a conjugated enolate (**49**). Care must be taken at this stage to avoid polymerisation and the hydrolysis was conducted rapidly to facilitate reprotonation of the enolate.



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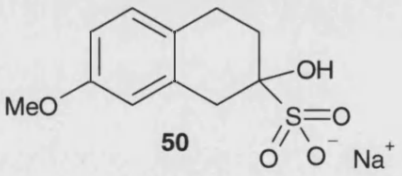


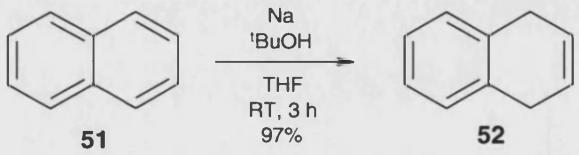
50

Purification of the crude tetralone was achieved *via* formation of the addition compound (**50**). Such compounds are readily formed from unhindered ketones and aldehydes by stirring the crude product with a saturated aqueous solution of sodium bisulfite.[101] The solid bisulfite adduct may then be separation by suction filtration and decomposed to the parent carbonyl compound by reaction with sodium carbonate solution. This proved to be an excellent method for purifying **35** and efficient washing at the filtration stage was found to afford a product of high purity by ^{1}H NMR after basic decomposition; further purification by reduced-pressure distillation was not considered to be necessary.

The highest yield of **35** obtained with the above procedure was 63%, consistent with literature values. This appears to suggest that only moderate yields of tetralone are possible with the present method. Additionally, the experimental procedure is somewhat tedious and time-consuming: the initial reduction stage where

pieces of sodium are dropped into refluxing ethanol *via* the condenser frequently takes in excess of an hour to perform and has obvious safety implications. It was therefore decided to investigate whether a more convenient, high-yielding procedure could be developed.

In a short paper published in 2003, Menzek *et al.*[102] reported a novel high-yielding procedure for the reduction of naphthalene (**51**) to 1,4-dihydronaphthalene (**52**), a reaction previously achieved using Na/EtOH at high temperatures. In this modified version, sodium is allowed to react with a solution of **51** in THF to form the corresponding radical anion which is subsequently quenched with *tert*-butanol to afford **52**. This "pre-formation" of the radical anion is an interesting contrast to the Na/EtOH technique where the anion is both formed and quenched simultaneously. The mild conditions and high yield (97%) also make it an attractive and convenient procedure. As the transformation of **51** to **52** can be considered to be analogous to **47** to **48**, it was decided to investigate whether the present synthetic method of **35** could be improved by incorporating features of this technique.



Scheme 8 (Novel reduction of naphthalene to 1,4-dihydronaphthalene[102])

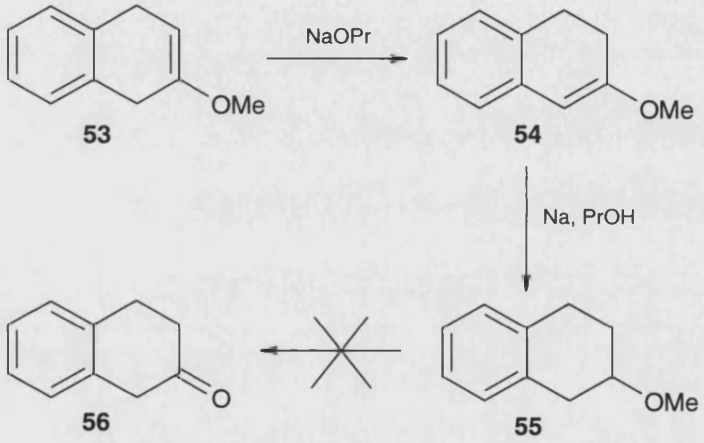
One of the most significant features of the Menzek procedure is that reduction is successfully effected at room temperature, being in direct contrast to the high (>80°C) temperatures required for the Cornforth technique. It was therefore decided to attempt reduction of diether **47** under similar conditions. Accordingly, 10 equivalents of sodium were added in small pieces to a solution of **47** in anhydrous THF at room temperature followed by an excess of *tert*-butanol. The mixture was stirred for 4 hours (until the sodium had completely reacted) and 5M HCl subsequently added. TLC analysis indicated that no reaction had occurred. An identical result was obtained when ethanol (which has a lower pKa) was substituted as the proton source. It is interesting to note that Menzek *et al.*[102] report a distinct blue colouration when the sodium is added to the naphthalene solution. No such

colour was observed with **47** as the substrate, suggesting that formation of the corresponding radical anion does not occur at room temperature. One way to rationalise this observation is that **47** is a more 'electron-rich' substrate than **51** due to the donating ether groups and therefore addition of an electron to **47** would be expected to have a higher energy barrier.

In order to further investigate this hypothesis, the reaction was repeated but the system heated to 60°C prior to addition of the alcohol. No colouration was observed, likewise suggesting the absence of a radical anion; however, TLC analysis after treatment with ethanol and subsequent hydrolysis with HCl showed that complete conversion to **35** had indeed occurred. It was consequently decided to repeat the process on a larger scale in order to compare the yield and quality of product with that obtained using the original method. 11g of **47** were carefully reacted under these conditions and subjected to the standard work-up procedure. This was found to result in a surprisingly high yield of **35** after purification through the bisulfite adduct (**50**). Analysis by ^{1}H NMR showed the product to be of high purity and several successive attempts consistently afforded improved yields (>80%) over the Cornforth method. The following additional advantages of the new experimental protocol were also noted:-

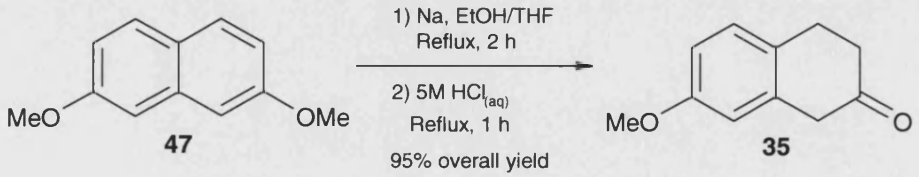
- As sodium does not react with THF or **47**, the required quantity of sodium may be added rapidly over a few minutes when the system is still at room temperature; the ethanol may then be added *via* a dropping funnel, leaving the user free to complete other tasks (however, care must be taken to maintain efficient stirring as the THF has a tendency to froth). Previously, addition of the sodium took nearly 1 hour and the reaction was considerably more vigorous.
- A significantly lower volume of ethanol is used which greatly facilitates the partitioning stage of the work-up (inseperable emulsions were common with the Cornforth method and the ethanol frequently had to be evaporated *in vacuo* before re-partitioning).
- Viscous brown material was often formed after the sodium addition stage with the previous method. This does not seem to occur with the modified procedure and the product possesses a cleaner overall appearance.

Menzek *et al.*[102] employ *tert*-butanol as the proton source due to its lower reactivity with sodium; this produces a slower, more controlled reduction process. The decision to replace *tert*-butanol with ethanol was a result of the findings of Cornforth who reported the yield of 2-tetralone to be inferior when propan-1-ol was used as solvent.[100] A possible explanation is that the initial 1,4-reduction product **53** rearranges to conjugated **54** in the presence of refluxing sodium propoxide solution. Further reduction can then occur to give **55** (Birch-type reactions do not normally reduce isolated double bonds), which is unable to hydrolyse to **56** (Scheme 9).



Scheme 9 (Rearrangement and further reduction of **53** in the presence of NaOPr)

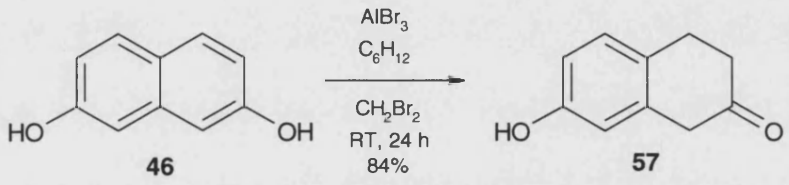
Evidence for the above hypothesis is provided by Menzek *et al.*[102], who report that naphthalene (**51**) reduces to 1,2,3,4-tetrahydronaphthalene with Na/^{t}BuOH under reflux *via* NaO^{t}Bu-induced rearrangement of 1,4-dihydronaphthalene (**52**). From this it can be postulated that sodium ethoxide does not possess a sufficiently high pKa to effect rearrangement (even at elevated temperatures) as the 1,4-reduction product is the sole one obtained.



Scheme 10 (Improved procedure for reduction of **47** to tetralone **35**)

In summary, a convenient and high-yielding procedure for the reduction of diether **47** to tetralone **35** (Scheme 10) has been developed. The yields obtained appear to be consistent and considerably greater than previously reported for this type of reduction. Further experiments to determine whether the new procedure is applicable to other mono- and dimethoxynaphthalene systems are planned.

During the optimisation of the above reaction, it was decided to concurrently investigate the work of Ostashevskaya *et al.*[103] who report an interesting one-step synthesis of 7-hydroxytetralone **57** from diol **46** (Scheme 11). This remarkable reaction is thought to proceed *via* an ionic hydrogenation mechanism involving abstraction of protons from cyclohexane with the assistance of aluminium bromide.



Scheme 11 (Reported ionic hydrogenation of 2,7-dihydroxynaphthalene[103])

The reaction appeared easy to perform: the reagents are simply dissolved in dibromomethane and the system allowed to stir for 24 hours at room temperature; however, repeated attempts to effect transformation of **46** using the reported procedure afford only a trace of product upon TLC of the quenched reaction mixture. The use of a different manufacturer's reagents, increasing the reaction temperature to reflux and even assistance from the author of the procedure still yielded no success. As a result of this and the relatively high cost of aluminium bromide, this method was abandoned and efforts focused on the Na/EtOH reduction procedure.

2.3.2 Synthesis of 2-amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol

Now that a suitable high-yielding route to precursor **35** had been identified, the remaining synthetic steps leading to aminotetralin **23** (see Scheme 4) could be investigated. Initially, introduction of a geminal dimethyl group at the 1-position of tetralone **35** was achieved by treating a solution of **35** in THF with sodium hydride, followed by iodomethane as alkylating agent. Subsequent reflux and aqueous work-

up gave a viscous brown oil which was purified by reduced-pressure distillation to afford low to moderate yields (<60%) of **36** as a light yellow liquid.

The method of Dailey *et al.*[104] reports that very high yields (91%) of the corresponding 6-methoxy analogue of **36** may be obtained using sodium hydride in benzene at room temperature; this latter condition is specifically stipulated as being necessary for a high yield. Application of this procedure to **35** (substituting toluene for benzene) afforded consistently greater yields (60-65%) of **36** after distillation, although the excellent yields reported by Dailey were not obtained. A viscous brown tar was observed to remain in the distillation vessel after collection of the product was complete; this was thought to be composed of aldol-like self-condensation products of **35** and probably contributed significantly to the diminished yield.

The existing procedures for the dimethylation of **35** appeared to be rather unsatisfactory: moderate yields were obtained but required tedious reduced-pressure distillation to separate the product from the residual tar (**36** cannot be purified by column chromatography due to its tendency to decompose on silica gel). In addition, analysis of the crude reaction mixtures by TLC indicated the presence of multiple alkylation products, suggesting that sodium hydride may not be the optimal base for this transformation. It was therefore decided to attempt the dimethylation of **35** under a range of alternative conditions (Table 5).

The primary aims of the investigation were to develop a robust procedure which selectively afforded the 1,1-dimethylation product **36** (*i.e.* did not lead to over-alkylation) in a suitably pure form such that further purification was not required (due to the aforementioned difficulties in purifying **36**). Consequently, the success of the reaction was determined using a combination of TLC and ^{1}H NMR analysis, and by visual inspection of the product obtained after work-up.

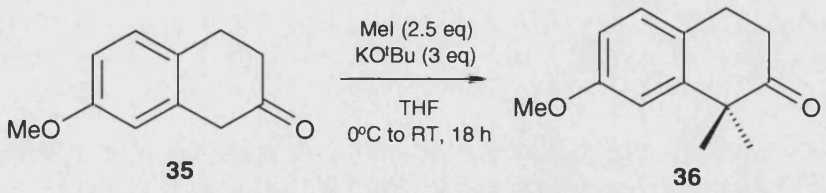
Hart *et al.*[105] report the successful dimethylation of **35** using sodium 2-propoxide as base. This result is somewhat contradictory to the studies of the methylation of phenylacetone by Suter *et al.*[106], who state that the use of sodium 2-propoxide leads to exclusive monomethylation. Nonetheless, it was decided to attempt the preparation of **36** using the original conditions described by Hart[105] and a slightly modified procedure (entries 3 and 4 respectively in Table 5). TLC analysis of the quenched reaction mixture showed a moderately clean reaction, although some starting material was clearly evident. The decision not to pursue this procedure further was a result of the commercial unavailability of sodium 2-propoxide,

necessitating its time-consuming (and somewhat hazardous) laboratory preparation by the reaction of sodium (or sodium hydride) with propan-2-ol.

In the same paper, Suter *et al.*[106] report that dimethylation of phenylacetone readily occurs in the presence of potassium *tert*-butoxide. As this base is inexpensive and readily available in its powdered form, it was decided to investigate its suitability as a replacement for sodium isopropoxide. A variety of conditions and solvents were tested and it was found that portionwise addition of 3 equivalents of KO^tBu to a solution of **35** and 2.5 equivalents of iodomethane in THF afforded a product of clean appearance (no viscous brown material observed) and high purity by ^1H NMR (entry 8 in Table 5 and Scheme 12).

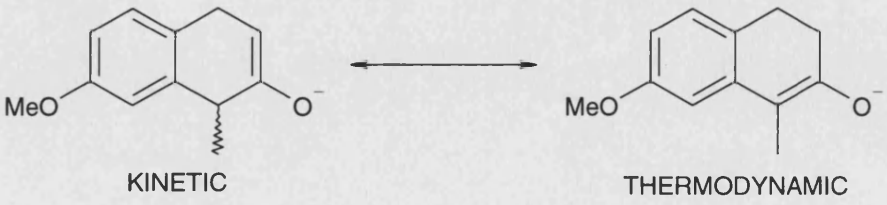
No	Reagents	Solvent	Order of addition	Conditions
1	NaH (4 eq) MeI (3.5 eq)	THF	NaH added to solution of **35** in THF followed by MeI	0°C to RT 3 h
2	NaH (3 eq) MeI (3 eq)	Toluene	**35** added to suspension of NaH in toluene followed by MeI	0°C to RT 18 h
3	NaO^iPr (10 eq) MeI (3 eq)	Propan-2-ol	**35** added to solution of NaO^iPr in propan-2-ol followed by MeI	0°C to rflx 2 h
4	NaO^iPr (3 eq) MeI (3 eq)	Propan-2-ol	**35** added to solution of NaO^iPr in propan-2-ol followed by MeI	0°C to rflx 3 h
5	KO^tBu (3 eq) MeI (3 eq)	DME	**35** added to mixture of KO^tBu and MeI in DME	RT 18 h
6	KO^tBu (3 eq) MeI (3 eq)	Toluene	KO^tBu added to solution of **35** in toluene followed by MeI	0°C to rflx 18 h
7	KO^tBu (2.3 eq) MeI (2.5 eq)	DME	KO^tBu added to solution of **35** and MeI in DME	0°C to RT 17 h
8	KO^tBu (3 eq) MeI (2.5 eq)	THF	KO^tBu added to solution of **35** and MeI in DME	0°C to RT 17 h

Table 5 (Conditions used to attempt dimethylation of tetralone **35**)



Scheme 12 (Dimethylation of tetralone **35**)

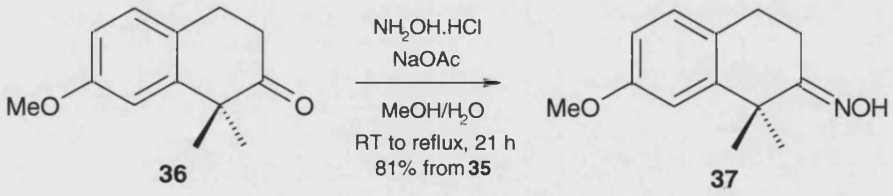
The decision to switch the order of addition of KO^{t}Bu and iodomethane was taken out of the need to minimise polymerisation of the enolate of **35**, a factor thought to be largely responsible for the presence of brown tar in the product. This technique effectively reduces the 'lifetime' of the enolate in the reaction mixture as it can rapidly react with the electrophile. One specific concern with this immediate alkylation method was whether rearrangement of the kinetic enolate would be able to occur rapidly enough to avert methylation at the 3-position; this applies particularly to the introduction of the second methyl group where deprotonation at the 3-position might be expected to be favoured due to the sterically-hindered nature of the *tert*-butoxide anion (Scheme 13). ^{1}H NMR studies of the product showed no indication of 1,3-dimethylation and TLC analysis revealed only trace amounts of the starting material and the 1-monomethylated product. Evidently, either rearrangement to the thermodynamic enolate occurs very rapidly due to the lower energy state afforded by conjugation with the aromatic ring, or the protons at the 1-position are so overwhelmingly more acidic that deprotonation at the 3-position does not occur to any significant extent with KO^{t}Bu. The fact that no products corresponding to tri- or tetraalkylation of **35** were detected suggests that a combination of both these two factors may be responsible.



Scheme 13 (Rearrangement of kinetic and thermodynamic enolates)

The quality of the product obtained using the new procedure was such that it could be used in the next stage of the synthesis without purification (in practice, **36** was always converted immediately to oxime **37** to avoid darkening of the material). The use of KO^{t}Bu instead of sodium hydride as base improves the safety and convenience of the process, allowing multigram quantities of **36** to be rapidly synthesised.

Conversion to the oxime **37** (Scheme 4) was readily achieved by treating **36** with hydroxylamine hydrochloride and sodium acetate according to the procedure previously used within the group. As **37** is insoluble in the MeOH/H_2O solvent system, it may be easily collected by suction filtration and dried for immediate use in the next stage. Additionally, trace impurities from the previous dialkylation step were not found to be present in the product oxime, affording **37** in an excellent state of purity. An improved yield was obtained if the reaction was first heated to reflux before stirring at room temperature (previously no heating was applied), and a 15g batch of **37** was successfully prepared in 81% yield from tetralone **35** using this method (Scheme 14). Unlike ketone **36**, oxime **37** was found to be highly stable and no signs of decomposition were found after storing at room temperature for several months.



Scheme 14 (Conversion of ketone **36** to oxime **37**)

An interesting effect of the geminal dimethyl group is that it appears to exert complete steric control over the configuration of the oxime group of **37**. The presence of both *syn* and *anti* isomers in a given sample are clearly revealed by ^{1}H and ^{13}C NMR spectroscopy as the oxime OH group causes a change in chemical shift of spatially proximal protons leading to 'doubling-up' of the signals in the NMR spectrum.[107] Examination of the ^{13}C NMR spectrum of **37** clearly indicates that only one isomer is present as 12 separate signals (corresponding to 12 chemical environments of **37**) appear in the spectrum. Given the steric crowding of the *syn*

isomer (Figure 7) and the efficient reduction of **37** to the corresponding aziridine (see Chapter 3), it is highly probable that the oxime exists in the *anti* form.

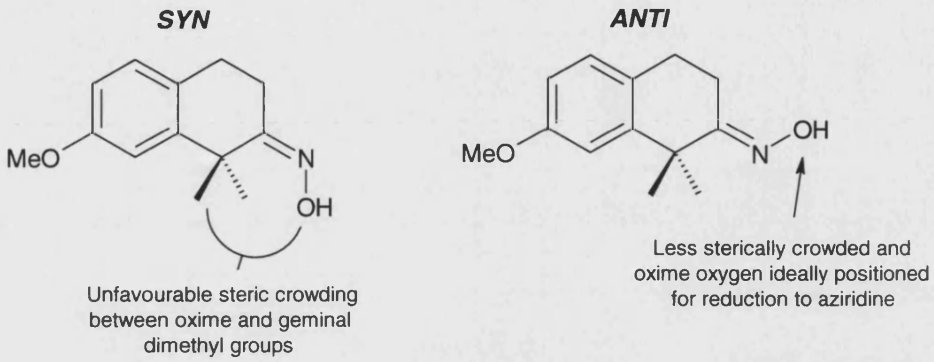


Figure 7 (Isomeric *syn* and *anti* forms of oxime **37**)

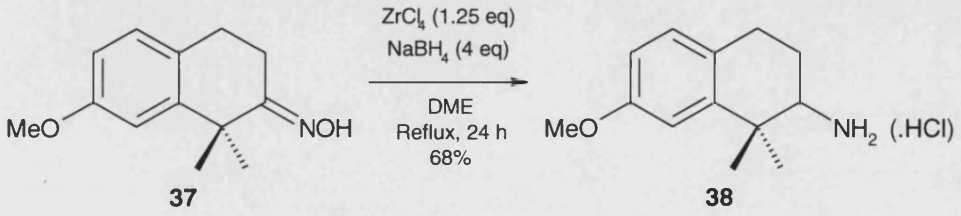
The reduction of oxime **37** to the primary amine **38** (Scheme 4) was initially carried out using 4 equivalents of lithium aluminium hydride in refluxing THF according to the method previously used within the group. TLC analysis of the crude reaction mixture after 24 hours at reflux revealed complete consumption of **37** and the presence of 3 product spots by UV (R_f values 0.34-0.60). Subsequent purification by column chromatography afforded the desired amine **38** in rather low 43-54% yields.

It is well established in the literature that the reduction of oxime groups to amines by $LiAlH_4$ is complicated by the formation of aziridines as side-products.[97] For this to occur, the molecule must possess a methylene or methyl group α to the oxime ; indeed, in cases where the methylene or methyl group is adjacent to an aromatic ring, the corresponding aziridine replaces the amine as the major reduction product. The low yields of **38** were primarily a result of such a side-reaction occurring (a phenomenon which was later exploited in Chapter 3). Additional drawbacks associated with the use of $LiAlH_4$ are its tendency to spontaneously ignite when first combined with the solvent and the inconsistent levels of activity between different batches of the reagent (on one occasion, a newly purchased batch was found to react slowly even with water!). Investigation of alternative reduction methods of **37** was therefore justified.

Attempts to effect reduction using 'non-hydride' reducing agents such as sodium in refluxing ethanol[108] and zinc in acetic acid[109] were unsuccessful. The combination of certain Lewis acids and sodium borohydride afford powerful reducing reagents and several examples have been reported in the literature as successfully reducing oxime functionalities to amines.[97,110,111] These systems appeared particularly attractive as the reducing species is generated *in situ*, thus avoiding the ignition hazards encountered with $LiAlH_4$. Additionally, the reported yields of amine are high and aziridines are not generated as side-products.

The $TiCl_4/NaBH_4$ system was initially chosen due to the ready availability of the reagents. Kano *et al.*[110] state that oximes may be readily reduced at room temperature with this system; however, no conversion of **37** was detectable by TLC analysis after 24 hours under these conditions. As discussed previously, the steric bulk of the *gem*-dimethyl group of **37** significantly attenuates reactions occurring at the 2-position and it appeared that this was the most probable reason for the lack of activity. Repetition of the reaction at reflux and subsequent TLC analysis indicated complete conversion to the amine **38**, though only a modest yield (57%) of product was obtained after acid extraction of the reaction mixture. The formation of emulsions arising from the presence of titanium salts significantly hampered the work-up process and was thought to be a major factor contributing to the low yield.

In view of developing a more convenient, higher-yielding procedure, the $ZrCl_4/NaBH_4$ system of Itsuno *et al.*[111] was also investigated. One particular disadvantage of $TiCl_4$ is its high degree of air sensitivity, which makes manipulation of the reagent somewhat troublesome; $ZrCl_4$, however, is a relatively stable solid and may be conveniently weighed on the bench. As with the previous system, **37** did not undergo reduction at room temperature with $ZrCl_4/NaBH_4$ in DME, but repeating the reaction at reflux afforded complete conversion.



37 **38**

Scheme 15 (Reduction of oxime **37** with $ZrCl_4/NaBH_4$)

An improved procedure for quenching the reducing agent was also devised, whereby the reaction mixture was treated with excess solid $NaSO_4.10H_2O$ (based on a similar procedure for the quenching of $LiAlH_4$[112]); this produced a granular precipitate of metal salts which were easily removed by suction filtration. Pure **38** was obtained as its HCl salt in improved 68% yield by subsequently treating the filtrate with propanolic HCl, evaporating the solvents and recrystallising the residue. This procedure represents a substantial improvement on the previous methods employed for this reaction as it is relatively free from hazards, uses inexpensive reagents, is easy to perform and requires no column chromatography.

The change in hybridisation of the 2-carbon has a significant effect on the ^1H NMR spectra of **37** and **38**. The presence of three sp^2 carbon centres in the B-ring of **37** forces it to adopt a rather strained conformation (Figure 8 → A) where four of the six C–C bonds are virtually planar. The geminal dimethyl protons are fixed in identical chemical environments (as shown by the accompanying Newman projection) and appear in the ^1H NMR spectrum as a single peak at approximately 1.20ppm integrating to 6 protons. Reduction of the oxime group causes a concurrent $sp^2 \rightarrow sp^3$ change in the hybridisation of the 2-carbon; the ring adapts by shifting to the energetically favourable 'half-chair' conformation[91,113] characteristic of the cyclohexenes (Figure 8 → B).

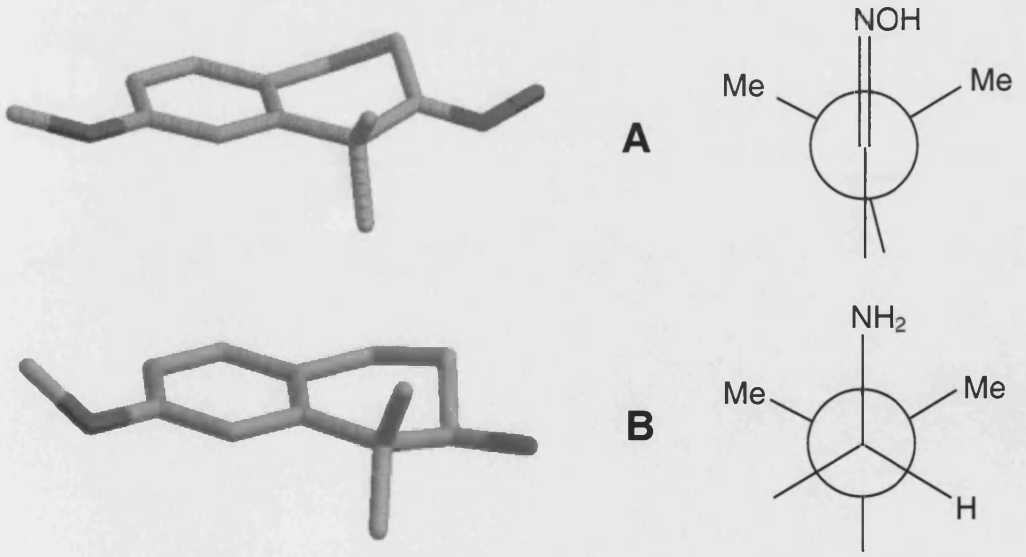
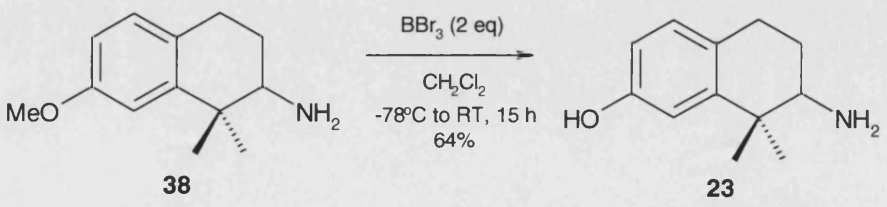


Figure 8 (Energetically favourable conformations of **37** (A) and **38** (B) with accompanying Newman projections of the $C_2 \rightarrow C_1$ bond - 3D structures generated using ChemSketch[114] and RasMol[115])

Examination of the corresponding Newman projection reveals that the methyl groups are now clearly in differing chemical environments - the consequence for the ^{1}H NMR spectrum is a change from one single peak to two peaks each integrating to 3 protons. This feature was observed in all subsequent spectra of compounds possessing the aminotetralin scaffold, although the separation of the two signals varied somewhat according to the *N*-substituent as the ring adapted to the lowest energy conformation.

The next step in the synthesis required the *O*-demethylation of the 7-methoxy group. A variety of methods for the cleavage of phenolic methyl ethers have been reported, of which the most established are concentrated hydrobromic acid[116], boron tribromide[117] and sodium propanethiolate.[118] Hydrobromic acid was initially selected for the *O*-demethylation of **38**, being the most convenient and economic method of the three. Methyl ether **38** was subsequently heated with 48% hydrobromic acid at 100°C for 3 hours; basification and standard work-up followed by column chromatography of the residue afforded the desired aminotetralin scaffold **23** in 40-60% yield. TLC analysis of the crude product often revealed a non-polar spot with a significantly higher R_f than the expected **23**. It is possible that a small proportion of HBr becomes oxidised to elemental bromine during the reaction (darkening of the reaction was observed to occur), which then reacts readily with the aromatic ring of **38** (or **23**) to form brominated side-products (flushing the system with nitrogen did not eradicate the problem, however).

A greater consistency of yield was achieved when *O*-demethylation was performed instead using 2 equivalents of boron tribromide in CH_2Cl_2 at −78°C.[117] Cautious quenching of the system with methanol followed by work-up as for HBr afforded consistent yields of **23** in excess of 65% after chromatography.



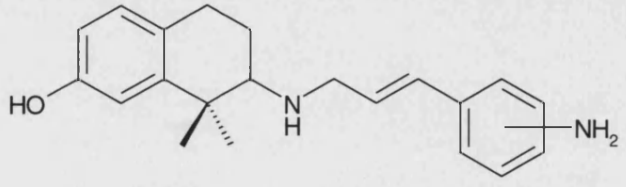
38 **23**

Scheme 16 (Methyl ether cleavage of **38** to afford aminotetralin scaffold **23**)

The use of boron tribromide as a reagent for the cleavage of methyl ethers has one distinct advantage over the other methods in that the reaction is performed under extremely mild conditions, considerably limiting the number of potential side-reactions. It is, however, a comparatively expensive and air-sensitive reagent which makes it rather inconvenient for multigram preparation of **23**. There is consequently still room for improvement in this synthetic step; recent experiments in the group utilising 10 mol% of tetra-*n*-butylammonium bromide in 48% HBr as a system for *O*-demethylation[119] have afforded promising results.

2.3.3 Synthesis of ring-substituted amines

The establishment of improved experimental procedures for the synthesis of intermediates leading to the aminotetralin scaffold **23** meant that sufficient material could now be prepared for the attachment of appropriate 'address' side-chains. It was discussed at the beginning of this chapter that the suitable positioning of an amine functionality *via* attachment to the terminal aromatic group of **26** may provide a means to enhance κ receptor selectivity. Primary amines **28-30** were proposed as the three key intermediates which, after obtaining preliminary pharmacological data, may be subsequently modified to afford ligands with 'address' amines of higher basicity (*e.g.* guanidines). During the preliminary work in the group on aminotetralin **23**, diversification at the primary amine group was achieved using a combination of direct alkylation and reductive alkylation methods. The particular choice of method depended primarily on the commercial availability and stability of the corresponding electrophiles. Direct *N*-substitution in this manner is clearly inappropriate for the preparation of **28-30**, as the exposed primary amine moiety is liable to react with the bromide/aldehyde group. It was therefore decided to use the corresponding nitro derivatives as masked amines for the initial coupling to scaffold **23**; reduction would then afford the desired ligands **28-30**.



28: ortho
29: meta
30: para

The synthesis of secondary amines by reaction with halides is generally difficult to achieve in satisfactory yield as the product readily undergoes further alkylation to afford tertiary (and often quaternary) amines.[97] This normally undesirable result was exploited in the preliminary work on **23** as it enabled mono- and disubstituted analogues to be readily prepared in one reaction. Since only monosubstituted ligands are required for the present investigation (the di-cinnamyl derivative of **23** displayed little activity in the binding assay), it appeared unwise to pursue this method of alkylation.

The reaction of a compound possessing an aldehyde or ketone group with a primary or secondary amine under dry conditions results in the elimination of water and formation of an imine (in the case of primary amines) or enamine (in the case of secondary amines). In reductive alkylation, the imine or enamine is subsequently reduced by catalytic hydrogenation or hydride reducing agents to furnish a secondary or tertiary amine respectively. Figure 9 illustrates this process.

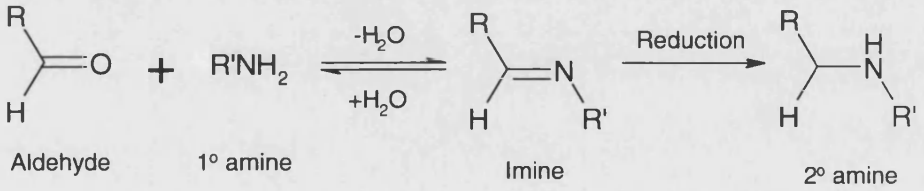


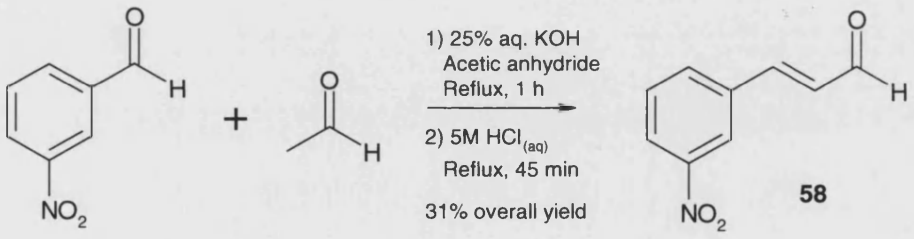
Figure 9 (Synthesis of secondary amines by reductive alkylation)

Modified reducing agents such as sodium cyanoborohydride and sodium triacetoxyborohydride selectively reduce imines in the presence of ketones or aldehydes, thus enabling imine formation and reduction to be achieved in a one-pot process.[97,120] As the resulting secondary amines are significantly more nucleophilic than the parent primary amines, further reaction generally occurs and tertiary amines are normally the major products. This technique was previously used in the group as an alternative to direct alkylation for the preparation of mono- and disubstituted derivatives of **23** in one reaction; it is not suitable, however, for the selective formation of monosubstituted ligands such as **28-30**.

The use of a two-stage reductive alkylation process for the synthesis of secondary amines has been reported in the literature.[121] The first stage involves reaction of the primary amine-containing compound with a slight excess of the

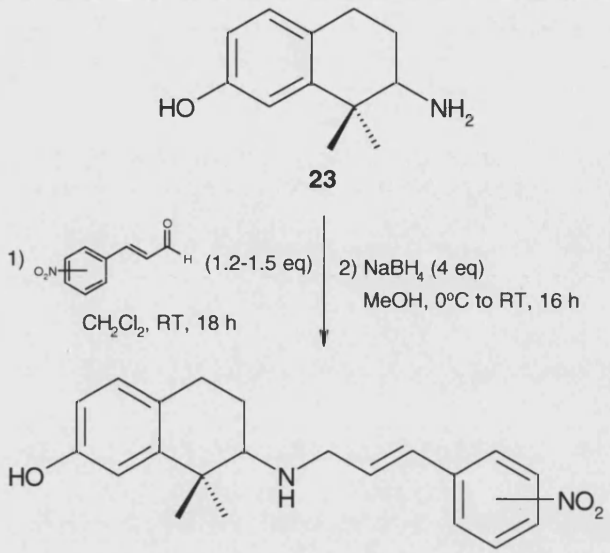
aldehyde or ketone to form the corresponding imine intermediate. Upon completion of the reaction, the crude mixture is treated with sodium borohydride which reduces both the imine and unreacted carbonyl, thus preventing further reaction and formation of tertiary amines. An alternative procedure for the synthesis of secondary amines has been reported by Mattson *et al.*[122] whereby the amine and carbonyl compound are combined in titanium(IV) isopropoxide and the resulting intermediate reduced with sodium cyanoborohydride; this method appeared to be somewhat more hazardous and inconvenient, however, and it was therefore decided to adopt the former procedure.

With the exception of 3-nitrocinnamaldehyde, the other aldehydes were conveniently available commercially in the *trans* form. 3-Nitrocinnamaldehyde (**58**) was obtained by direct condensation of 3-nitrobenzaldehyde with acetaldehyde in 31% yield according to a known procedure[123] (Scheme 17).



Scheme 17 (Synthesis of 3-nitrocinnamaldehyde[123])

Reaction of the nitrocinnamaldehydes with **23** to form the corresponding imines was carried out in CH_2Cl_2 at room temperature. This was followed by evaporation of the solvent and treatment of the crude mixture with 4 equivalents of $NaBH_4$ in methanol; aqueous work-up and purification by column chromatography afforded excellent yields of the secondary amines **59-61** (Table 6). Curiously, the imines derived from *meta*- and *para*-nitrocinnamaldehydes precipitated out of the reaction as they formed and were found to be only sparingly soluble in methanol leading to very poor yields after reduction. This problem was solved by the addition of a small quantity of DMF (see Table 6) which efficiently solvated the imines, enabling reduction to the desired secondary amines to occur readily.



No	Position	Reduction solvent	Yield
59	ortho	MeOH	83%
60	meta	4:1 MeOH/DMF	86%
61	para	4:1 MeOH/DMF	81%

Scheme 18 and Table 6 (Reductive alkylation of **23** with nitrocinnamaldehydes)

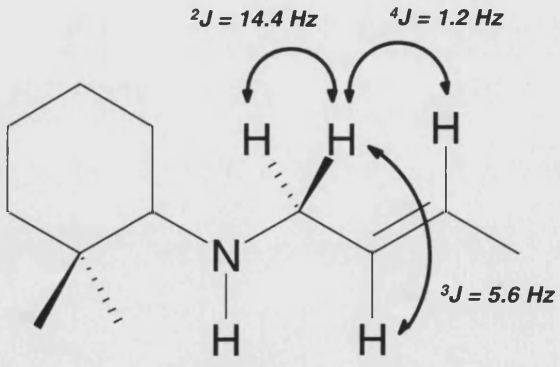
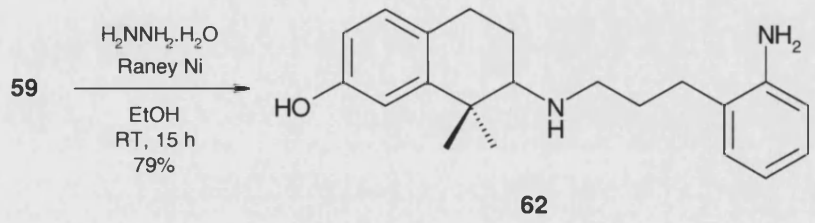


Figure 10 (Diastereotopism of the methylene protons in **61**)

The partial structural rigidity of the nitrocinnamyl side-chain is amply demonstrated by the ^{1}H NMR spectra of **59-61**. The lack of free rotation about the alkene bond causes the allylic methylene protons to become diastereotopic and appear on the spectrum of as two distinct 'doublet of doublet of doublets' at 3.44 and

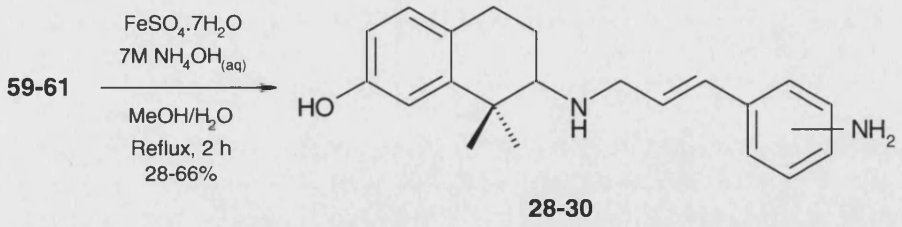
3.69 ppm (for **61**). The three observed coupling constants for the methylene protons of **61** are rationalised in Figure 10; one noticeable feature is the presence of long-range (^4J) coupling characteristic of such allylic systems.

Completion of the synthesis of **28-30** required unmasking of the aromatic nitro group to afford the primary amine. A vast array of methods are available for the reduction of aromatic nitro groups utilising a wide range of both elemental metals and their salts.[97] The Raney nickel/hydrazine hydrate reduction system had been previously applied within the group for such transformations and has the additional advantage of being effective under mild conditions. Treatment of the *ortho* derivative **59** according to the method of Brown and Nelson[124] at room temperature afforded a clean reaction with only one product apparent by TLC. Purification by column chromatography and subsequent NMR analysis, however, showed that over-reduction to the saturated compound **62** had occurred (Scheme 19). It was decided to submit this compound for biological testing in order to investigate how a greater degree of conformational freedom in the address side-chain would affect the pharmacological profile.



Scheme 19 (Raney Ni/hydrazine hydrate results in over-reduction of **59**)

Attempted reduction of **59** using iron powder in acetic acid at reflux afforded a mixture of products including a significant proportion of **62** which proved difficult to remove during purification. Cuerva *et al.*[125] report that iron(II) sulfate heptahydrate in aqueous ammonia reduces aromatic nitro groups at reflux. Treatment of **59** using this method was found to successfully afford the desired unsaturated amine **28** in satisfactory 66% yield after purification. The remaining amines were obtained in a similar manner, although a degree of over-reduction was observed for the *para* derivative resulting in a diminished yield of 28%.



Scheme 20 (Successful iron(II) sulfate/ammonia reduction of **59-61**)

The purified ligands **28-30** were converted to their respective HCl salts (as described in Chapter 7) and submitted for pharmacological evaluation. A sample of *ortho*-NO_2 derivative **59** was also submitted as excess material was available (unfortunately, sufficient quantities of the *meta* and *para* analogues **60** and **61** for testing were unavailable and would have required complete re-synthesis).

At this point in the project, increasing focus was being placed on the investigation of 3-methoxy-substituted ligands (see Chapter 3) and it was therefore decided to delay synthesis of analogues of higher basicity (*e.g.* guanidines) until the *in vitro* pharmacological data on compounds **28-30** had been received. These results became available close to submission of this thesis and there was unfortunately insufficient time to further expand on the series. However, the improved procedures leading to key intermediates **28-30** should enable larger quantities of these compounds to be rapidly synthesised and consequently provide a robust starting point for further investigations.

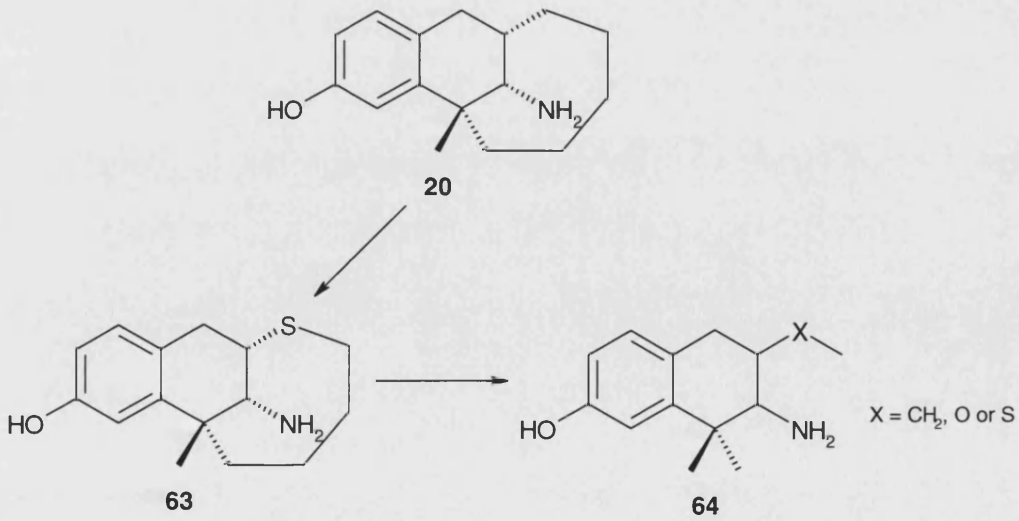
CHAPTER 3

INVESTIGATION OF 3-METHOXY ANALOGUES OF 2-AMINO-1,1-DIMETHYLTETRAHYDRONAPHTHALEN-7-OL

3.1 Design rationale

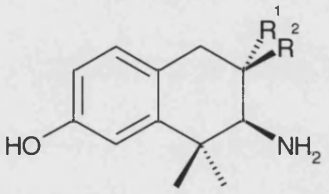
Whilst conducting the initial stages of the work directed towards the synthesis of aromatic primary amine derivatives **28-30** (see p. 49), a novel series of aminotetralin ligands for opioid receptors were independently disclosed in a letter by Caroline Roy and her associates.[126] The design of the ligands was again inspired by dezocine (**20**), but a different approach was taken in the structural simplification which is of significant interest to the present project.

In an effort to obtain opioid analgesics with superior potency to **20**, the corresponding thioether derivative **63** was synthesised. Subsequent binding and antinociceptive assays showed that **63** possessed a high degree of μ receptor binding and significant analgesic ability. Presumably recognising that exclusion of the bridging ring could provide a series of ligands with a somewhat simpler synthesis but retaining affinity for opioid receptors (in a similar manner to the design rationale of aminotetralin scaffold **23**), thioether **63** was further simplified to the non-bridged structure **64**.



Scheme 21 (A series of structurally simplified analgesics based on dezocine[126])

A series of analogues of **64** possessing different substituents at the 3-position were synthesised and tested for opioid binding. Table 7 shows the data obtained for a selection of the more active compounds. It should be noted that the compounds were prepared and submitted as their racemic *cis* and *trans* forms - the stereochemistry given is merely to demonstrate the isomer being referred to.



		K_i (nM)		
R^1	**R^2**	**μ**	**δ**	**κ**
H	SCH_3	286	Not tested	Not tested
SCH_3	H	1.1	349	66
H	CH_2CH_3	135	Not tested	Not tested
CH_2CH_3	H	21	4507	345
OCH_3	H	1.8	5216	184

Table 7 (Binding assay results for selected compounds reported by Roy *et al.*[126])

One particularly striking feature of this series is the considerable difference in μ binding affinity between corresponding *cis* and *trans* isomers of compounds bearing the same 3-substituent: comparison of the μ affinities for the two isomers of the 3-thiomethyl derivative (Table 7: *cis* $R^2 = SCH_3$, *trans* $R^1 = SCH_3$) indicates a 260-fold increase in μ receptor binding when the 3-thiomethyl substituent is *trans* relative to the primary amine moiety. From these results it appears that an additional residue on the receptor may be enhancing ligand binding under certain conditions - a *trans* relationship between the amine and 3-substituent may facilitate the greatest degree of interaction between each of the two groups and its corresponding binding site on the receptor; a *cis* arrangement, on the other hand, may allow one group to interact but place the other at too far a distance from its target site on the receptor. The enhanced analgesic potency of the *trans* isomer compared to the *cis* form is somewhat unexpected given that dezocine (**20**) possesses a *cis* relationship between the bridging ring and the primary amine at the 2-position.

Of the three substituents tested, thiomethyl (SCH_3) confers greatest affinity at μ, δ and κ opioid receptors. The methoxy (OCH_3) derivative exhibits an almost equal degree of binding at the μ receptor, though with a substantial loss of affinity at the δ and κ receptors. The ethyl (CH_2CH_3) substituted analogue is the pharmacologically least significant of the three, exhibiting only moderate affinity for the μ receptor (but significantly lower than SCH_3 and OCH_3) and poor affinities for the δ and κ receptors. No explanation for the high μ affinity of the SCH_3 and OCH_3 analogues is provided by the authors of the paper and the results do not appear to correlate with any clear trend in electronegativity, hydrogen-bonding ability or other factor which might enhance ligand-receptor interaction.

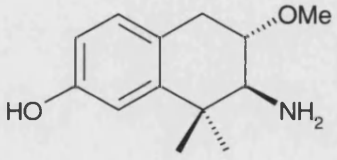
In summary, the above results indicate that an SCH_3 or OCH_3 group at the 3-position in general affords superior opioid receptor binding affinity for aminotetralins of structure **64**, though only when the substituent is orientated *trans* to the primary amine moiety. These findings are of great interest to the present project, as one of the major aims was the investigation of possible structural alterations to the 'message' scaffold **23** in view of obtaining ligands with superior affinities for opioid receptors. One particularly attractive feature is that inclusion of an SCH_3 or OCH_3 substituent to the scaffold would not significantly increase the overall size of the ligand, thus retaining the desired 'small molecule' criterion which is pivotal to the current project.

The use of 3-substituted aminotetralin **64** as a scaffold on which to construct opioid antagonist ligands was not established in the report of Roy *et al.*[126], as the primary focus of the work was on the development of potent μ agonists for use as analgesics. The preliminary work on scaffold **23** in the group has already shown that simple secondary and tertiary amine derivatives behave purely as opioid antagonists, despite the structure of **23** being directly derived from the agonist dezocine (**20**). This evidence, together with the potential pharmacological ramifications already discussed, gives strong support to the synthesis and biological assay of an equivalent 3-substituted series of compounds.

Whilst Table 7 indicates that the SCH_3-substituted analogue possesses the highest affinity for all three receptor types, it was decided after consideration to instead utilise the OCH_3-substituted aminotetralin as the starting point for the present investigation. The major factor in this decision was the synthetic route to this particular analogue reported by Roy and co-workers[126] is two steps shorter than the

corresponding SCH_3 derivative. As the OCH_3 analogue exhibited an almost equally high affinity for the μ receptor as the SCH_3 compound and moderate affinity for the κ receptor, it was concluded that the use of an OCH_3 3-substituent would be more than sufficient to enable the pharmacological ramifications of including such a group at the 3-position to be evaluated whilst necessitating a shorter and hence more attractive synthesis than the corresponding 3-SCH_3 aminotetralin.

In order to investigate how a 3-OCH_3 substituent in aminotetralin **23** would affect the ability of *N*-substituted derivatives to function as pure opioid antagonists, it was decided to synthesise a series of compounds based on modified scaffold **65** possessing simple alkyl *N*-substituents. This would allow direct comparison to the series previously synthesised in the group derived from original scaffold **23**, enabling the effect of the 3-OCH_3 group on opioid receptor affinity and selectivity to be firmly established.

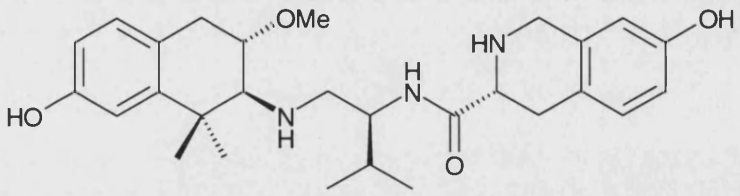


65

Proposed N-substituents:

Cinnamyl
Allyl
n-Propyl
Cyclopropylmethyl
1-Phenylpropyl

It was discussed in Chapter 1 that the combination of the tetrahydroisoquinoline side-chain utilised in JDTic (**14**) and novel aminotetralin scaffold **23** was found to afford a potent and selective κ antagonist (**27**, p. 24), though less potent than **14** itself. Given that inclusion of a 3-OCH_3 group has the potential to increase receptor affinity in derivatives of **23**, it was decided that synthesis of the corresponding 3-OCH_3 analogue of **27** would be an interesting addition to the studies of the alkyl derivatives of **65**. If successful, **66** may prove to be a useful research tool as an alternative to norBNI (**10**) and JDTic (**14**) for studies of the κ opioid receptor. Separation of the two diastereomers of **66** (since the valine and tetrahydroisoquinoline units are chirally pure) was also of interest in order to compare the effects of the two aminotetralin *trans* isomers on the pharmacological profile of the ligand and expand the structure-activity information of the series.

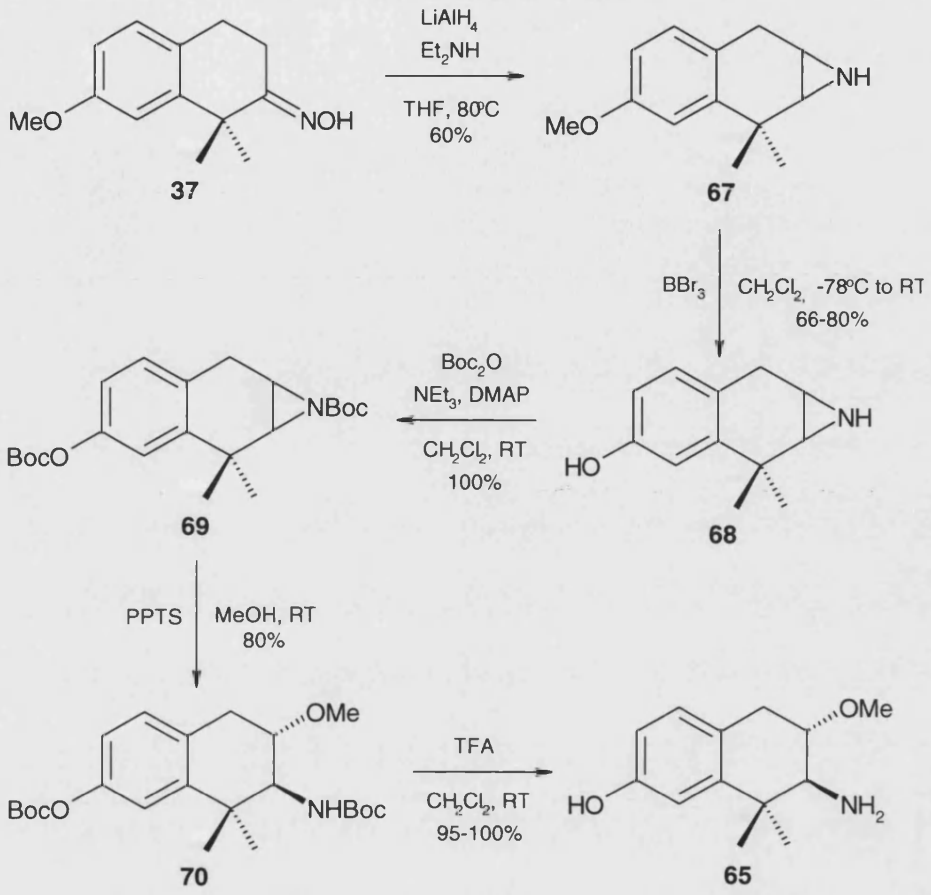


66

3.2 Overview of literature synthetic route

Roy *et al.*[126] report that the preliminary test compounds (in Table 7) were prepared as mixtures of *cis* and *trans* isomers by direct alkylation of 1,1-dimethyl-7-methoxy-2-tetralone (**36**, p. 31) with the appropriate electrophile (the exception to this was the OCH_3 analogue which was prepared exclusively by the new method described below) followed by conversion to the primary amine *via* the oxime; column chromatography was then used to separate the mixtures into *cis* and *trans* forms. As it became apparent that the *trans* isomers had greater opioid receptor affinity, a new synthetic route was devised utilising an aziridine ring-opening reaction which selectively afforded the desired *trans* forms. Scheme 22 illustrates the synthetic route used to obtain *trans*-3-methoxyaminotetralin **65** (Scheme 22), though unfortunately the actual experimental procedures were not disclosed in the original paper.

The synthesis of 3-methoxyaminotetralin **65** begins with the commercially available 7-methoxy-2-tetralone (**35**) which is subsequently dimethylated and converted to oxime **37** (Scheme 4) in a similar manner to that described for aminotetralin **23**. Usefully, the two synthetic routes share the common intermediate **37** whose synthesis has already been optimised as described in Chapter 2. Aziridine **67** represents the most important intermediate in the synthesis of **65**, as it is the means by which the crucial *trans* relationship between the 3-methoxy group and the primary amine moiety is established. The conditions used to transform oxime **37** to aziridine **67** are rather interesting as the system which is employed, $LiAlH_4$ in refluxing THF, is one of the standard methods to reduce oximes to primary amines (up to 55% yields of **38** were previously obtained from **37** using this method). It was discussed in Chapter 2 that aziridines are frequently observed side-products of $LiAlH_4$ reductions; in this case the presence of diethylamine in the reaction mixture appears to reverse the outcome of the reaction so that **67** is the major product (in 60% yield) rather than the primary amine **38**.



Scheme 22 (Literature synthesis of 3-methoxyaminotetralin **65**[126])

Aziridine **67** is subsequently *O*-demethylated using boron tribromide to afford phenol **68** in 66-80% yield. This is followed by acylation of the aziridine nitrogen and phenol with Boc_2O affording the activated aziridine species **69**. Acid-catalysed ring-opening with methanol under mild conditions introduces the required *trans* stereochemistry to yield **70** as a mixture of the two enantiomers. Finally, facile Boc deprotection with trifluoroacetic acid affords a quantitative yield of the 3-methoxyaminotetralin **65**.

As the majority of the steps in the synthesis of **65** given by Roy *et al.*[126] appeared relatively straightforward, it was decided to pursue this route for the preparation of the proposed ligands. The availability of alternative routes to **65** is somewhat hampered by the requirement of the 2,3-*trans* stereochemistry; aziridine ring-opening therefore appears the only feasible option in this case. It should be noted that Boc protection of the phenolic moiety was originally undertaken to

provide a common intermediate (**69**) for the synthesis of other analogues[126] (notably SCH_3) but is superfluous in the preparation of **65**; however, it was decided to adhere to the original scheme so as to compare and improve the yields of all steps.

3.3 Synthetic studies

3.3.1 Synthesis of 3-methoxyaminotetralin scaffol

Until recently, the use of aziridines as intermediates in organic synthesis has been largely neglected due to the lack of convenient preparative methods for this functional group. This situation is rapidly changing, however, and is primarily a result of the considerable progress being made in nitrene-transfer methods of aziridine synthesis which allow direct preparation from alkenes.[127] Much effort has also been applied to the development of asymmetric catalysts for these reactions[128-130], and it appears likely that in the near future the aziridine group will rival the epoxide in terms of synthetic accessibility and applications in organic synthesis.

The preparation of aziridines by the hydride reduction of oximes in the literature is largely confined to a small number of papers submitted by Kotera *et al.*[107,131-133] in the 1960's and a brief investigation by Landor and colleagues[134] in 1974. Aside from these reports, the method appears to have been almost completely abandoned and in a recent review of aziridine chemistry[127], it was noticeably absent from the list of viable synthetic methods. Although it cannot be denied that the nitrene-transfer preparation of aziridines from alkenes offers greater potential in terms of superior yields and stereoselectivity, there will be occasions in organic synthesis where introduction of an alkene moiety is not feasible and it is desirable to have an alternative means by which to introduce the aziridine functional group. Further exploration of this reaction with the specific aim of improving the 60% yield of intermediate **67** reported by Roy *et al.*[126] was therefore conducted.

Due to the inconsistent and somewhat hazardous nature of $LiAlH_4$, it was decided to investigate the use of the related reducing agent sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH or Red-Al®), shown previously by Landor *et al.*[134] to lead to superior yields in this type of reaction. SMEAH is a derivative of $LiAlH_4$ with similar reactivity but is non-pyrophoric[135] and therefore considerably safer than $LiAlH_4$; this is a particular concern when designing a suitable procedure to obtain multigram quantities of the aziridine. Whereas the experimental

procedure of Landor *et al.*[134] advocates the use of THF as solvent, it was initially decided to attempt the conversion of oxime **37** to aziridine **67** in solvents of higher boiling point. This decision was based on the finding that elevated temperatures were required to effect reduction of **37** to primary amine **38** with the $ZrCl_4/NaBH_4$ system (see p. 46), despite the literature examples specifying room temperature as being sufficient.[111] This was taken as an indication of the considerable steric obstruction of the 1,1-dimethyl group of **37** on the carbon atom of the neighbouring oxime, inhibiting the approach of nucleophiles to the 2-position.

As SMEAH is supplied as a solution in toluene, it appeared logical to attempt the reaction in this solvent as it is of relatively high boiling point and immiscible with water which facilitates aqueous work-up. Treatment of a solution of **37** in toluene with 5 equivalents of SMEAH and 10 mol% diethylamine (see below) followed by 18 hours at reflux afforded a 35% yield of aziridine **67** after acid/base work-up and column chromatography. The product was easily characterised as an aziridine by the two peaks at 2.12 and 2.47 ppm in the ^1H NMR spectrum - each integrated to 1 proton and exhibited a vicinal coupling constant of 6.2 Hz, indicating a *cis* relationship[136] between the protons at the 2 and 3 positions. TLC analysis showed that a significant amount of starting material and primary amine was present in the crude product. It was thought that poor solubility of oxime **37** could be contributing to the low yield of **67** and the reaction was therefore repeated using varying mixtures of toluene and the more polar solvent DME (Table 8).

Solvent	Auxiliary amine	Eq. Red-Al	Yield
Toluene	Diethylamine	5	30%
Toluene	*N*-Methylbutylamine	5	35%
1:1 DME:Toluene	*N*-Methylbutylamine	4	45%
1:1 DME:Toluene	4-Dimethylaminopyridine	4	47%
2:1 DME:Toluene	*N*-Methylbutylamine	4	55%

Table 8 (Effect of solvent and auxiliary amine on yield of aziridine **67**)

The results obtained show that increasing solvent polarity increases the yield of aziridine. This may be a result of either improved solubility of **37** or increasing solubility of the intermediate aluminium complex according to the reaction mechanism presented by Landor *et al.*[134] (Figure 11). They proposed that formation of the aziridine **67** over the primary amine **38** depends on elimination of the AlR_2HO^- fragment in the initial transition state to form an unsaturated nitrene species; effective solvation of the aluminium complex aids its elimination and consequently favours the pathway of aziridine formation. Kotera *et al.*[131] also found yields of aziridine to be considerably greater when the reduction was conducted in THF and DME rather than diethyl ether, providing support for this theory.

The addition of a catalytic quantity of a secondary amine to the reaction mixture has been briefly reported by Kotera *et al.*[131] to more than double the yields of aziridine when $LiAlH_4$ is used as the reducing agent. The reason for this is not clear and no subsequent studies are reported in the literature, though it has been established that the effect of auxiliary amine substitution on yield of aziridine is of the order: secondary > primary > tertiary. These results strongly suggest that a nucleophilic mechanism is involved. Interestingly, there is no mention of the use of a catalytic amine in the later work of Landor *et al.*[134] on SMEAH reduction of oximes; however, it was decided to incorporate an auxiliary amine into the present experimental investigation as there was no apparent reason that it should not exert a similarly beneficial effect on the yield of aziridine **67**. The use of *N*-methylbutylamine[131] instead of diethylamine gave rise to a slightly increased yield of **67**; this may be a consequence of the higher boiling point of *N*-methylbutylamine (90°C) over diethylamine (56°C) resulting in proportionally less existing in the vapour phase at any one time. The hypernucleophilic catalyst 4-dimethylaminopyridine (DMAP) was not found to significantly improve the yield of **67** compared to *N*-methylbutylamine, though whether increasing nucleophilicity exerts an effect on the overall rate of reaction remains to be elucidated. This, together with the testing of further secondary amines with the aim of discovering a superior catalyst, was to be the subject of further study although unfortunately this could not be accomplished within the time restraints.

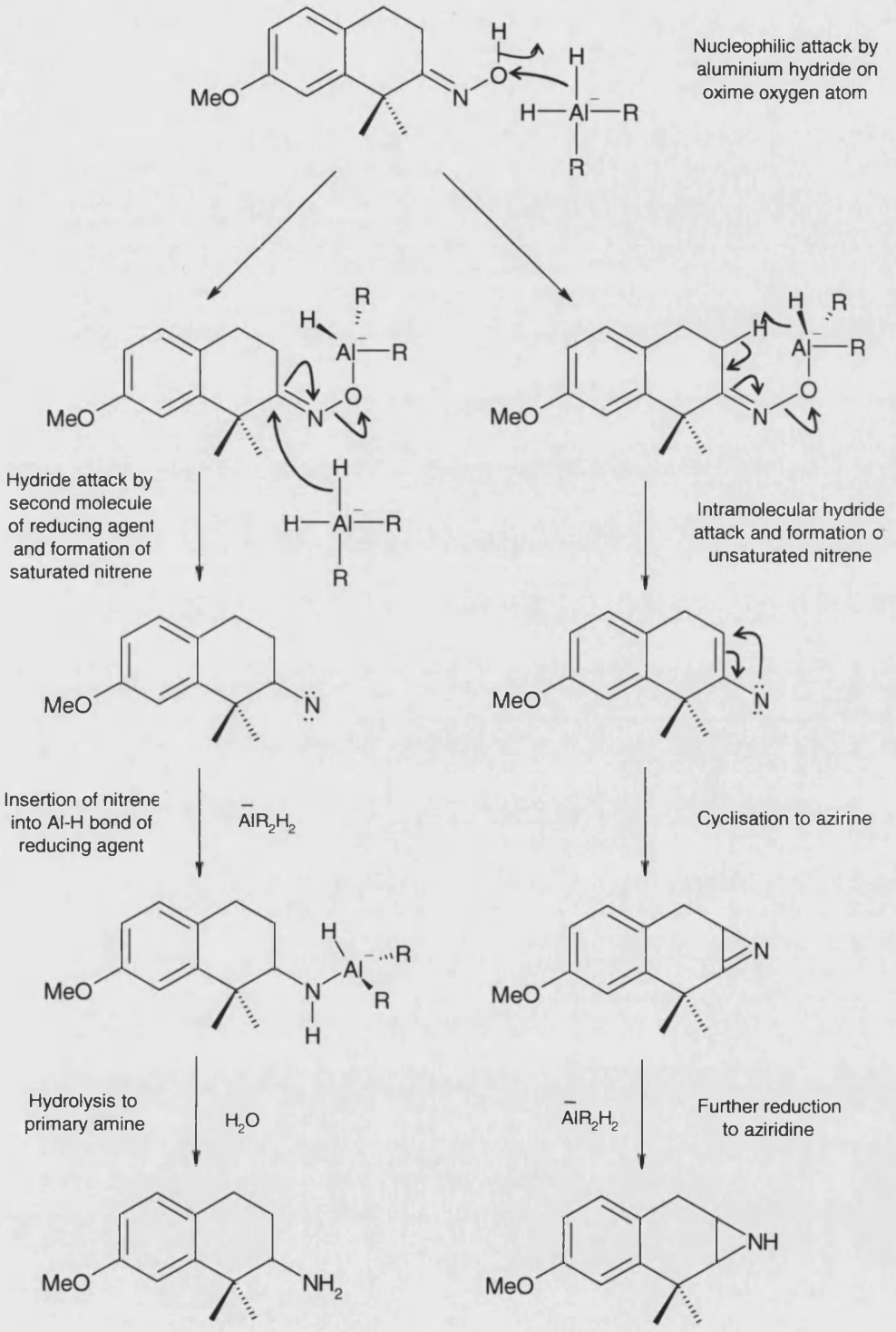
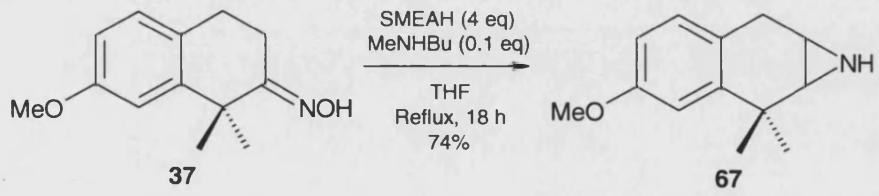


Figure 11 (Proposed mechanisms for formation of primary amine **38** and aziridine **67** by hydride reduction of oxime **37** adapted from Landor *et al.*[134])

The effect of solvent on yield of **67** (Table 8) indicated that solubility of oxime **37** and/or the intermediate aluminium complex (Figure 11) was of greater importance than the gain in reaction temperature afforded by the use of toluene. It was therefore decided to attempt reduction of **37** in 100% THF. In an effort to make the procedure more convenient, the addition was carried out in reverse: a solution of the oxime in THF was introduced to the reaction vessel containing SMEAH *via* a dropping funnel; this replaced the rather tedious dropwise addition of viscous SMEAH solution *via* syringe. This was found to result in consistently high (>70%) yields of **67** exceeding the 60% conversion quoted by Roy *et al.*[126] (Scheme 23); in addition this method was easier to perform, less hazardous (no $LiAlH_4$) and the reaction was very clean requiring only facile purification to remove the small quantity of primary amine side-product (**67** can be obtained in an excellent state of purity by a "dry-column chromatography" technique[112] which requires only minimal amounts of silica gel).



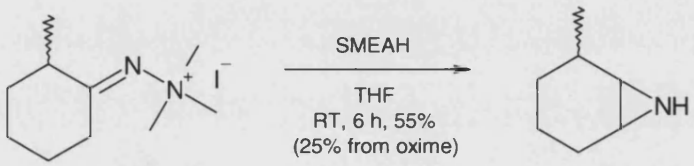
37 **67**

Scheme 23 (Improved reduction of oxime **37** to aziridine **67**)

One final investigation was carried out in an attempt to further improve the yield of aziridine **67**. Inspired by the theory of Landor *et al.*[134] regarding the dependence of aziridine yield on the ability of the complex transition state to be effectively solvated (see Figure 11), it was thought that solubility of the aluminium complex might be further increased by addition of a crown ether to the reaction mixture. Crown ethers are effective phase-transfer catalysts which have a wide application in organic synthesis. Their catalytic effect arises from their ability to surround certain cations (particularly Na^+ and K^+) resulting in a diffuse positive charge which markedly increases the solubility of both the cation and accompanying anion in organic solvents.[97] It was thought that chelation of Na^+ ions in the reduction of **37** might lead to a concomitant increase in the solubility of the negatively charged transition state. To test this hypothesis, reduction of **37** was conducted with the

addition of 10 mol% of 15-crown-5 to the reaction mixture. A 77% yield of **67** was obtained after purification - this was not considered to be a significant gain on the 74% yield afforded without 15-crown-5 and consequently no further investigations were carried out.

A rather interesting variation on the hydride reduction of oximes to aziridines has been described by Girault *et al.*[137,138] They reported that *N,N,N*-trimethylhydrazonium salts such as **71** could be reduced with SMEAH under mild conditions to the aziridine **72** (Scheme 24) in greater yields than that obtained from reduction of the corresponding oxime. It was therefore considered worthwhile to evaluate this method as an alternative route to **72**.



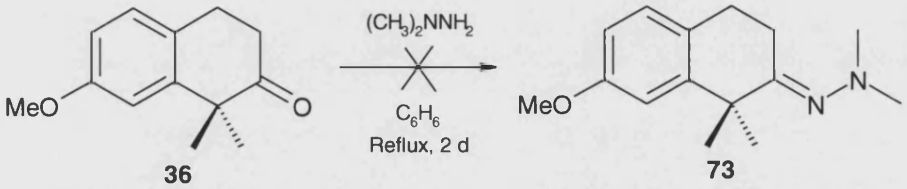
71 **72**

Scheme 24 (Alternative preparation of aziridines from *N,N,N*-trimethylhydrazonium salts[137])

Although no explanation is given for the increased preference shown for the aziridine over the primary amine, one possible reaction pathway might be "deprotonation" of the methylene group adjacent to the hydrazone by intermolecular attack of aluminium hydride resulting in formation of an unsaturated nitrene intermediate which subsequently cyclises to aziridine **72** *via* the azirene. Approach of aluminium hydride to the hydrazone carbon and formation of primary amine *via* the saturated nitrene is disfavoured as a result of the steric hindrance imparted by the quaternary ammonium centre.

Preparation of *N,N,N*-trimethylhydrazonium salts has been achieved in the literature by the condensation of a carbonyl compound with *N,N*-dimethylhydrazine, followed by treatment with iodomethane to give the quaternary salt.[139] Using this methodology, a solution of ketone **36** in benzene was treated with excess *N,N*-dimethylhydrazine and the system heated at reflux with azeotropic collection of water. Unfortunately, conversion to hydrazone **73** could not be achieved after 2 days at reflux (Scheme 25) and TLC analysis showed only starting material. It is highly

likely that this is again a result of the steric hindrance imparted on the 2-carbon by the proximal dimethyl group. Utilising a sealed tube system or conducting the reaction under solvent-free conditions may afford better results, but the success of the improved SMEAH oxime reduction method and the highly toxic nature of *N,N*-dimethylhydrazine led to this route being abandoned.



Scheme 25 (Failed conversion of ketone **36** to *N,N*-dimethylhydrazone **73**)

After formation of aziridine **67**, the next stage in the synthesis of aminotetralin **65** was *O*-demethylation to give the corresponding phenol **68** (Scheme 22). The number of available methods to effect this transformation is severely restricted by the presence of the aziridine moiety. As discussed in Chapter 2, strong protic acids such as HBr are a facile way to cleave aromatic methyl ethers; exposure of aziridines to such acids, however, leads to protonation of the nitrogen and subsequent ring-opening by the halide (Figure 12). The use of highly nucleophilic thiolates at elevated temperatures also affords ring-cleavage products.

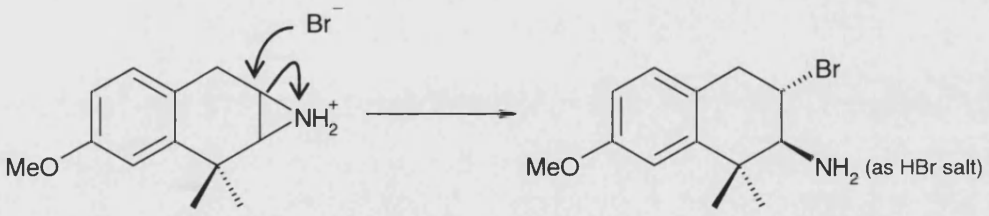


Figure 12 (Exposure of aziridines to strong protic acids leads to ring-opening)

It appeared that boron tribromide was the only feasible option and therefore **67** was treated according to the procedure applied to *O*-demethylation of **38** using this reagent. The yields obtained were rather inconsistent (40-70%) and TLC analysis indicated the presence of numerous side-products on most attempts. As the residue obtained after quenching with methanol was distinctly acidic, it appeared that

acid-induced cleavage of the aziridine may be a possible cause of side-product formation. In an attempt to prevent this, the reaction was instead quenched by pouring over a mixture of concentrated ammonia and ice though this gave similarly disappointing yields. Far superior results were obtained by the dropwise addition of a 1:4 mixture of the stronger base triethylamine and methanol at –78°C. This consistently afforded high (>75% yields) of phenol **68** and minimal side-products by TLC.

Efficient Boc-acylation of the phenolic and aziridine moieties of **68** was achieved using catalytic DMAP to afford **69** (Scheme 22) in high yield. The major role of the Boc group here is not one of protection from electrophiles but activation of the heterocycle towards ring-opening. The diminished electronegativity of nitrogen compared to oxygen means that aziridines are less susceptible to ring-cleavage than epoxides.[127] Direct nucleophilic ring-opening of *N*-unsubstituted aziridines requires high temperatures and the products are liable to participate in polymerisation reactions unless the attacking species is of high nucleophilicity. At elevated temperatures there is also likely to be an accompanying loss of regioselectivity. These difficulties can be largely averted by the use of a suitable aziridine activating group, of which the most widely utilised are carbonyl (esp. Boc) and sulfonyl (esp. Ts) types.[127] Ring cleavage may then be effected under very mild conditions using a wide range of nucleophiles[140] including alcohols[141], water[142], amines[143] and halides[144]; high regioselectivity is normally observed for these reactions and the primary amine moiety resulting from cleavage remains masked and consequently cannot participate in further nucleophilic reactions.

The remarkable way in which aziridine activating groups transform the conditions required for ring-opening has been attributed to two factors.[127] Crucially, the electron-withdrawing nature of these groups provide a *kinetic* activation by enhancing the polarisation of the C-N bond; this in turn increases the partial positive charge on the aziridine carbon atoms, thus making the ring considerably more susceptible to nucleophilic attack. Of secondary importance but significant in the case of carbonyl activating groups is a *thermodynamic* effect resulting from delocalisation of the amide-like anion produced after ring-cleavage. These effects are illustrated in Figure 13.

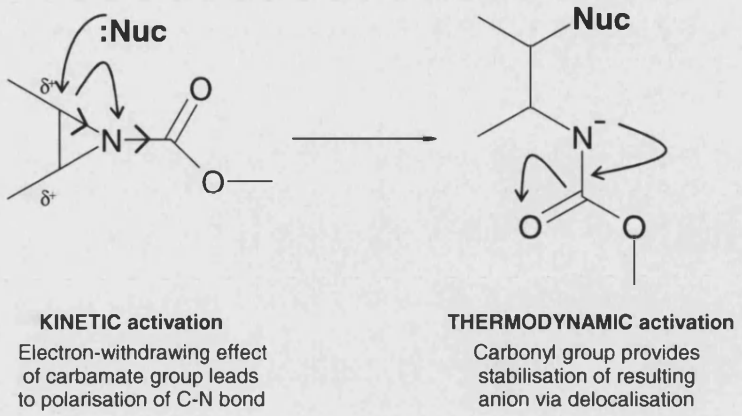


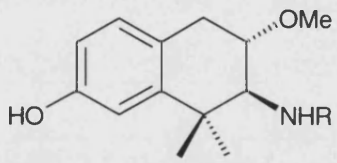
Figure 13 (*N*-substituents activate aziridines by kinetic and thermodynamic mechanisms)

Cleavage of activated aziridines is normally conducted in the presence of a catalyst in order to eradicate the need for heating and maximise regioselectivity. An enormous range of such catalysts have been investigated to effect ring-opening including protic acids[140], Lewis acids[141,143] and cyclodextrins.[145] Different catalysts appear to favour different classes of nucleophile and there is consequently no 'universal catalyst' for aziridine ring-opening available. For conversion to **70** (Scheme 22), Roy and co-workers[126] utilised the weak acid pyridinium *para*-toluenesulfonate (PPTS) which presumably acts simply *via* protonation of the aziridine nitrogen (it should be noted that delocalisation of the nitrogen's lone pair does not occur to any significant extent in **69** due to the additional ring-strain which would result from the resonance isomer); thus the aziridine is now sufficiently activated to enable attack even by the weak nucleophile methanol. This appeared to be an inexpensive and very convenient method for ring cleavage and consistently afforded high (80%) yields of **70**. The 1,1-dimethyl group plays a crucial role in the high yield by inhibiting approach of methanol to the 2-carbon, resulting in a completely regioselective reaction with no trace of the other isomer apparent by TLC. One puzzling aspect of this reaction was that between 10-20% starting material was consistently recovered during purification. Complete consumption of **69** could not be achieved even after stirring for several days, heating at reflux or adding excess catalyst; the reason for this is unclear. An alternative method using boron trifluoride diethyl etherate as catalyst[141] gave inferior yields of **70** and the formation of side-products was evident by TLC.

The synthesis of 3-methoxyaminotetralin **65** was completed by Boc deprotection of the phenolic and amine moieties of **70**. This was readily achieved in quantitative yield using an excess of trifluoroacetic acid which afforded **65** in a state of sufficient quality by NMR that purification was deemed to be unnecessary. The ^{1}H NMR spectrum of **65** clearly confirms the required *trans* relationship between the 3-methoxy group and the primary amine moiety by the presence of a vicinal coupling constant of ~10 Hz[136] between the 2-CH and 3-CH protons.

3.3.2 Synthesis of alkyl N-substituted analogues

The attachment of *N*-substituents to the aminotetralin scaffold **65** to afford the desired ligands was achieved using a variety of synthetic methods (Table 9).



No	R	Electrophile	Method	Yield
74	Cinnamyl	PhCH=CHCHO	A	82%
75	Cyclopropylmethyl	$(CH_2)_2CHCHO$	B	23%
76	Allyl (mono)	$CH_2=CHCH_2Br$	C*	50%
77	Allyl (di)	$CH_2=CHCH_2Br$	C*	35%
78	n-Propyl	$CH_3(CH_2)_2Br$	C	43%
79	n-Propylphenyl	$Ph(CH_2)_3Br$	C	54%

*obtained in same reaction

Reagents and conditions: (A) i) RCHO, CH_2Cl_2, RT ii) $NaBH_4$, MeOH, 0°C to RT; (B) RCHO, $NaB(OAc)_3H$, DCE, RT; (C) RBr, Na_2CO_3, cat. TBAI, THF, Reflux

Table 9 (Alkylation methods used to synthesise ligands **74-79**)

The stepwise reductive alkylation method of secondary amine synthesis which was successfully used to obtain aminotetralin derivatives **28-30** (p. 49) initially appeared an attractive route to the desired alkyl analogues of **65** due to the mild conditions employed and the absence of side-products resulting from over-

alkylation. As expected, treatment of **65** with *trans*-cinnamaldehyde readily gave the corresponding imine which was reduced with $NaBH_4$ to cleanly afford **74** in high yield. During the preliminary work on alkyl derivatives of aminotetralin **23**, the CPM derivative was obtained in 69% yield over two steps by acylation of **23** with cyclopropanecarbonyl chloride followed by $LiAlH_4$ reduction. As CPM-aldehyde is also commercially available, it appeared worthwhile to investigate whether reductive alkylation might provide an alternative and slightly more convenient route to this analogue. Unfortunately, treatment of **65** with cyclopropanecarboxaldehyde did not produce a clean reaction and several decomposition products were visible by TLC. The poor results were most likely caused by a lack of stabilising groups on the aldehyde: in situations where the aldehyde group is conjugated to an aromatic ring, as is the case for cinnamaldehyde, the resulting imine is normally highly stable and may often be isolated[97] (such compounds are known as Schiff bases). For simple saturated aldehydes no such stabilisation is present and decomposition and/or polymerisation often rapidly occurs.[97] Better results were obtained when 1.5 equivalents of CPM-aldehyde and the selective reducing agent sodium triacetoxyborohydride[120] were introduced in rapid succession at the start of the reaction in order to immediately 'capture' the imine and prevent decomposition. This afforded **75** in 23% yield after chromatography, although a significant quantity of starting material (**65**) and other side-products were evident by TLC.

In view of the disappointing yields obtained by reductive alkylation, it was decided to search for a suitable alternative method for the synthesis of the remaining analogues. This was particularly necessary for the allyl derivative as competing Michael reactions between acrolein (the corresponding aldehyde) and the primary amine group of **65** would further reduce the yield. The allyl analogue of **23** was previously prepared in the group by direct alkylation with allyl bromide in DMF which gave the mono- and dialkylated forms in 41% and 15% yield respectively. The formation of quaternary ammonium compounds was prevented by using a base of sufficient weakness ($NaHCO_3$) so as to discourage over-alkylation; it is also probable that steric hindrance imparted on the amine moiety by the 1,1-dimethyl group disfavours alkylation beyond the tertiary stage.

A different protocol for direct *N*-alkylation has been proposed by de Sousa *et al.*[146] for the selective *N*-dialkylation of amino alcohols. Tertiary amines were obtained in high yield by refluxing the amino alcohol with the relevant bromide,

sodium carbonate and catalytic tetra-*n*-butylammonium iodide in THF. It was reported that longer reaction times and several equivalents of base were required to afford tertiary amines using unreactive alkyl bromides; this suggested that good yields of the corresponding secondary amines might be obtained by careful monitoring of the reaction and quenching before significant over-alkylation to the tertiary amine occurred. The choice of solvent also made this method somewhat more appealing than the one previously employed as THF is significantly less harmful and easier to remove than DMF.

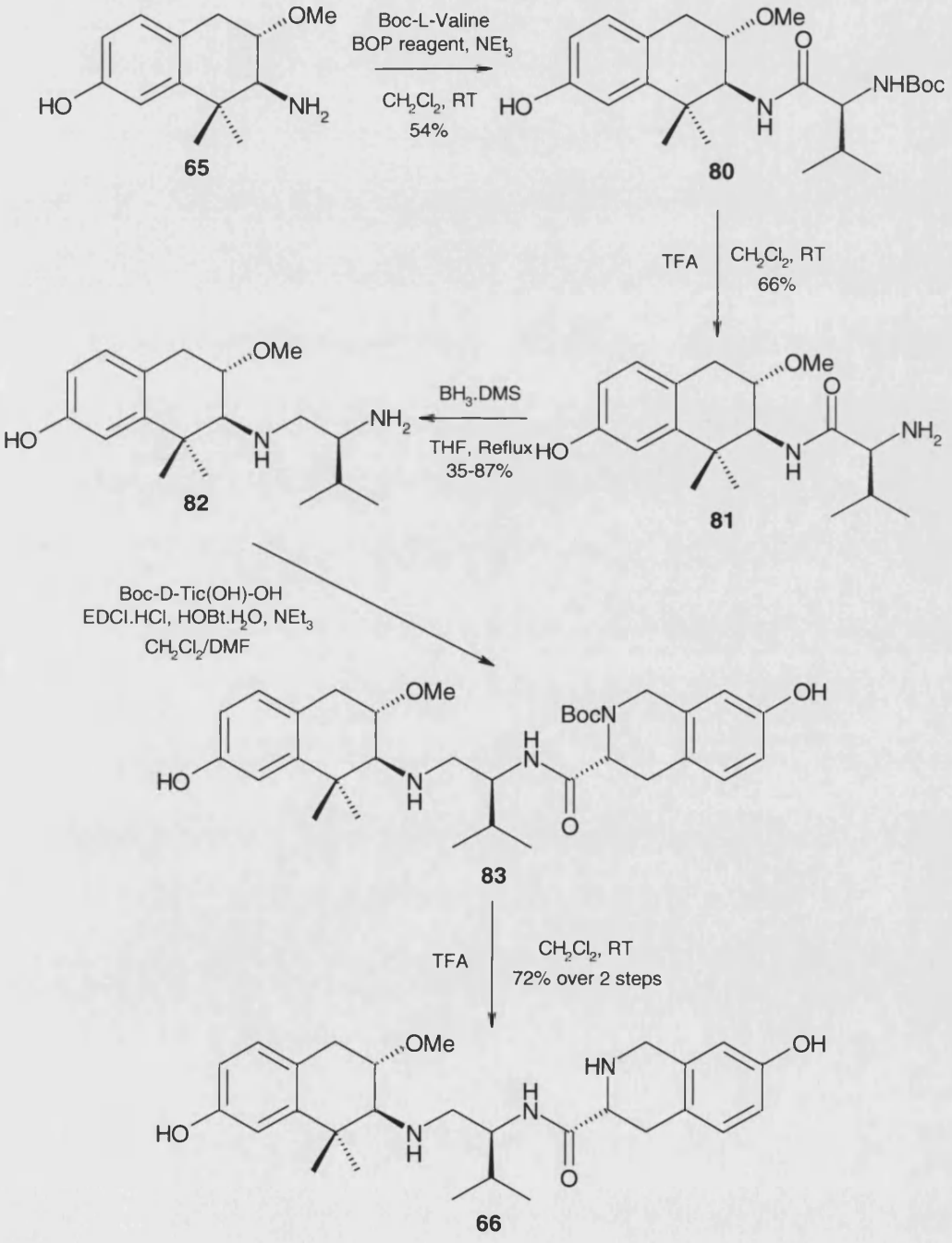
Alkylation of **65** with allyl bromide was performed according to the original procedure of de Sousa *et al.*[146] although the reagent proportions were altered to bias the outcome of the reaction in favour of the secondary amine product (Table 10). Complete consumption of the starting material was apparent by TLC after 24 hours, at which point the reaction was terminated. Subsequent column chromatography afforded the mono- (**76**) and dialkylated (**77**) products in 50% and 35% yields respectively. A significant proportion of **77** was expected on the basis of the high reactivity of allyl bromide, although the yield of both products remained superior to those obtained using the $NaHCO_3$/DMF procedure. As expected, the less reactive *n*-propyl and *n*-propylphenyl bromides required prolonged reflux and additional portions of halide and base were added to reduce reaction times. Satisfactory yields of **78** and **79** were obtained, although it should be noted that starting material was still apparent by TLC in both cases when the reactions were terminated; it is therefore highly likely that the yields quoted could be improved. In summary, this alkylation method has proved to be a convenient route for the one-step preparation of alkyl analogues of **65**. It is also notable that no dialkylated products or those resulting from phenolic alkylation were isolated in the case of **78** and **79**.

No	R	Eq. bromide	Eq. Na_2CO_3	Eq. TBAI	Time
76 + 77	Allyl	1.6	2.5	0.2	24 h
78	n-Propyl	2.2	3.5	0.5	68 h
79	n-Propylphenyl	2.5	4.0	0.5	60 h

Table 10 (Proportions of reagents required for RBr/Na_2CO_3/TBAI alkylation of **65**)

3.3.3 Synthesis of tetrahydroisoquinoline 'JDTic' compound ***66***

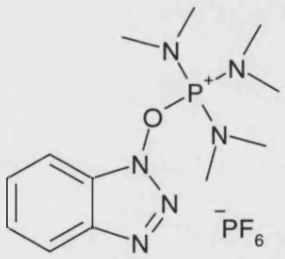
The synthetic route initially utilised to prepare ligand **66** possessing the identical 'address' side-chain to JDTic (**14**, p. 17) was adapted from the combinatorial approach to *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidinyl analogues described by Thomas *et al.*[74,76] (Scheme 26).



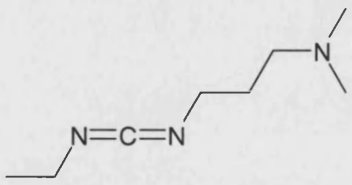
Scheme 26 (Initial route to **66** adapted from the combinatorial approach of Thomas *et al.*[74,76])

Construction of the side-chain was achieved by sequential coupling and Boc deprotection of two amino acid residues, with an intermediate reduction step to preserve the basic nature of the aminotetralin amine group.

The synthesis of amides is frequently achieved by conversion of a carboxylic acid to an acyl chloride, followed by direct reaction with an amine under mildly basic conditions. Whilst successful for relatively simple alkyl achiral carboxylic acids, this method is largely unsuitable for sensitive acids or those possessing chiral centres, and a range of peptide coupling reagents have been developed to facilitate direct amide synthesis from the amine and carboxylic acid under mild conditions.[147] The underlying mechanism of all such coupling reagents is initial formation of an active ester from the carboxylic acid and coupling reagent. This is followed by attack of the amine on the ester which is promoted by displacement of the activating group to give a stable side-product and the desired amide. The DCC/HOBt combination remains the most widely used system for peptide coupling, although phosphonium salts (*e.g.* BOP[148], **84**) and other carbodiimide reagents (*e.g.* EDCI[149], **85**) are also popular.



84



85

Figure 14 (Peptide coupling reagents)

The active esters derived from phosphonium salts are more reactive than the corresponding ones derived from DCC and consequently attack by the amine nucleophile occurs before any significant degree of racemisation can take place. This makes reagents such as **84** particularly suitable for amide formation using chiral carboxylic acids and as such was employed by Thomas *et al.*[74,76] for the synthesis of JDTic (**14**). Coupling of aminotetralin **65** to Boc-L-Valine using this procedure afforded moderate (54%) but consistent yields of amide **80**; some degree of ester formation resulting from reaction of the phenolic group of **65** was also apparent by TLC. Analysis of the ^{1}H NMR spectrum showed a 1:1 mixture of diastereomers,

though no separation could be achieved by either TLC or column chromatography. **80** was then treated with trifluoroacetic acid under the standard conditions for Boc cleavage to afford the corresponding amine **81**.

It was discussed above that reduction of the amide moiety of **81** was required in order to restore the basic nature of the aminotetralin nitrogen atom. In keeping with the procedure described by Thomas *et al.*[74], **81** was treated with borane.DMS complex which was expected to smoothly afford the diamine **82**. Unfortunately, inconsistent yields were obtained (35-87%) and the crude reaction mixture was frequently found to contain numerous side-products with similar R_f's to the desired product **82**. The reason for this was not clear, and the use of fresh borane and strict adherence to the literature procedure failed to give a more consistent outcome. Attempted reduction of **81** using $LiAlH_4$ afforded similarly poor results, as did $ZrCl_4/NaBH_4$.

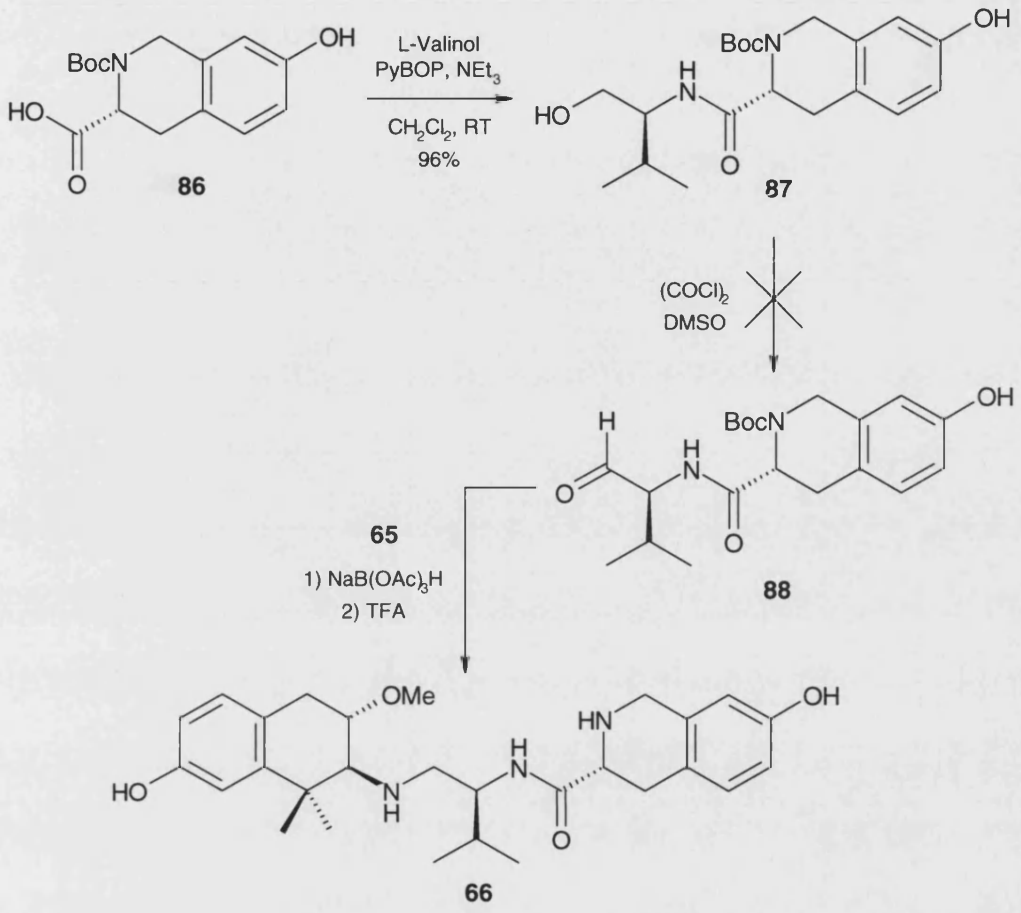
Introduction of the tetrahydroisoquinoline (Tic) 'address' moiety was again achieved using peptide coupling chemistry. Treatment of **82** with commercially availabile Boc-D-Tic(OH)-OH and BOP (**84**) afforded the required amide, though due to the polar nature of **83** separation of the tris(dimethylamino)phosphine oxide by-product of BOP (**84**) by column chromatography proved to be rather troublesome. Repetition of the reaction employing the related coupling reagent PyBOP also resulted in a significantly contaminated product. It was at this point that attention turned to the carbodiimide EDCI (**85**) as a potential solution to this problem. A particularly attractive feature of this reagent is that both the parent carbodiimide and its by-product are soluble in water[149], allowing easy removal by aqueous washing. Thus **82** was coupled to Boc-D-Tic(OH)-OH using EDCI.HCl and HOBt (required in this case to accelerate the reaction and so minimise racemisation of the chiral amino acid). TLC analysis indicated a significantly cleaner reaction and the desired **83** was obtained after chromatography. A very minor trace of side-product was evident by ^1H NMR, though it was decided to delay further purification until the final stage of the synthesis in order to minimise loss of material. Treatment of **83** under standard Boc cleavage conditions afforded the desired ligand **66** (Scheme 26) which was obtained free of contamination in 72% yield (over two steps) after facile column chromatography. Unfortunately, diastereomeric separation could not be achieved at any point in the synthesis and the intermediate compounds were always isolated as 1:1 mixtures. As a consequence of this, the ^1H and ^{13}C NMR spectra are complex

and difficult to interpret with the majority of signals appearing twice (except those atoms distant from the diastereomeric centres). The use of different chromatographic solvent systems similarly failed to produce any observable degree of separation and it was therefore decided to submit **66** for pharmacological evaluation as a mixture of diastereomers. Studies are currently being conducted elsewhere in the group to evaluate the use of chiral derivatising agents in the enantiomeric separation of aminotetralins **23** and **65**.

The synthetic route adopted for the preliminary synthesis of ligand **66** (Scheme 26) is purely linear in its approach and involves a total of 14 steps from 2,7-dihydroxynaphthalene (**46**). Such linear syntheses suffer from considerable overall loss of material and are less time-efficient than convergent routes as each synthetic step must be carried out sequentially. One additional concern with the former route was the unreliable borane reduction of the intermediate amide **81**. With this in mind, it was decided to examine whether a convergent approach to **66** might be feasible.

A highly desirable improvement to the existing procedure would be to construct the tetrahydroisoquinoline side-chain as a separate unit to the scaffold **65**; coupling of the two fragments and subsequent Boc-deprotection would then afford the completed ligand **66**. This route would appear to be more efficient as aminotetralin **65** and the side-chain could be synthesised in parallel, which decreases both the time required and the total number of linear steps. The proposed synthetic route is given in Scheme 27. In view of the difficulties encountered during reduction of amide **81**, it was decided to forgo the use of peptide coupling chemistry for this reaction in favour of a reductive alkylation approach which would directly afford secondary amine **83** and eliminate the need for amide reduction. It was envisaged that the required aldehyde **88** would be synthesised by coupling of Boc-D-Tic(OH)-OH (**86**) to L-valinol to give alcohol **87**; mild oxidation would then afford **88**.

Amino acid **86** successfully underwent peptide coupling with commercially available L-valinol in the presence of PyBOP to cleanly afford **87** in 96% yield. However, it was found that the product was virtually insoluble in most organic solvents and a poor ^{1}H NMR spectrum was obtained even in DMSO-d_6. This caused severe difficulties in the next stage and attempted oxidation of **87** under the Swern conditions (oxalyl chloride in DMSO) resulted in a mixture of many products. It was thought that interaction of the phenolic group of **87** with the oxidising agent may also have contributed to the poor outcome of the reaction.

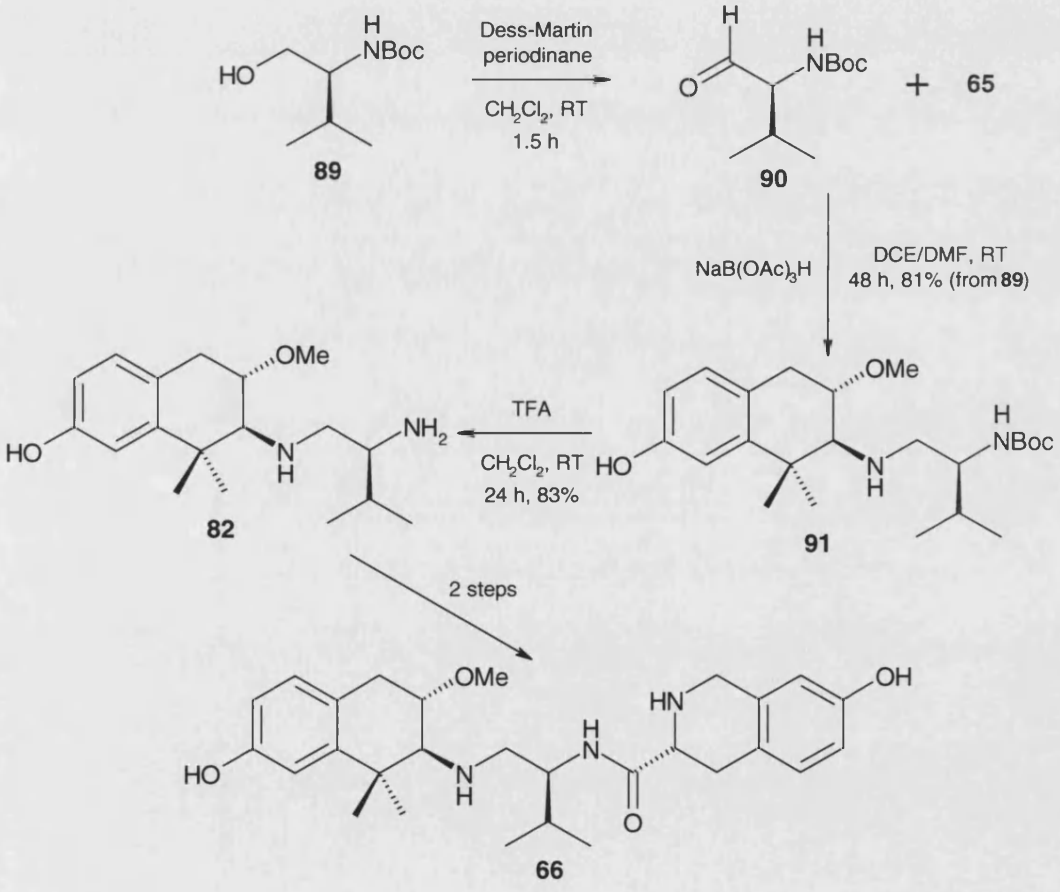


Scheme 27 (Proposed convergent synthesis of ligand **66**)

It appeared that the difficulties encountered with the oxidation of **87** might be at least partially overcome by suitable protection of the phenolic group. A protecting group of high lipophilicity would confer greater solubility in organic solvents in addition to preventing interaction of the phenolic group with oxidising agents. The trityl (triphenylmethyl) protecting group appeared ideal for this purpose as it possesses a very high degree of lipophilicity and may be removed under acidic conditions (thus enabling it to be cleaved concurrently with the Boc group). Reaction of **86** with triphenylmethyl chloride and DMAP afforded a satisfactory (63%) yield of the trityl-protected amino acid; however, subsequent coupling with L-valinol gave poor results and TLC of the crude product suggested that decomposition had occurred. A possible explanation for this is that the carboxylic acid moiety promoted a form of 'self-deprotection' of the trityl group in the solution phase. It is possible this problem may be overcome by the use of a more acid-stable protecting

group such as triisopropylsilyl (TIPS), but in view of the difficulties already encountered with this reaction pathway it was decided to investigate other alternatives.

Although it appeared that an unconvoluted synthesis of aldehyde **88** may not be possible, the use of reductive alkylation to introduce the valine unit still appeared an attractive solution to the problematic amide reduction. An alternative approach was therefore proposed (Scheme 28) whereby the valine fragment would be introduced in its *N*-protected form by reductive alkylation; this would be followed by deprotection and coupling of the Tic unit using EDCI.HCl as per the original (Scheme 26) synthesis.



Scheme 28 (Improved synthetic route to ligand **66**)

The initial step involved oxidation of the commercially available Boc-L-valinol (**89**) to the corresponding aldehyde **90**. The reagent selected to perform this transformation was the Dess-Martin periodinane[150], a hypervalent iodine compound which has found wide application in organic synthesis for the selective oxidation of alcohols to aldehydes. It possesses the advantages of high yields of aldehyde, simple experimental protocols and mild reaction conditions; the latter making it particularly suitable for the oxidation of highly functionalised and sensitive substrates. Treatment of **89** with 1.5 equivalents of Dess-Martin periodinane at room temperature was found to rapidly afford the required aldehyde **90** after 1.5 hours (monitored by TLC). Due to the often sensitive nature of aldehydes, it was decided to react **90** immediately with aminotetralin **65** without purification. Accordingly, a slight excess of **90** was combined with **65** in 4:1 DCE/DMF (**65** was found to be poorly soluble in pure DCE) and the mixture immediately treated with excess sodium triacetoxyborohydride. TLC analysis of the crude product after aqueous work-up indicated a very clean reaction, and a pleasing yield (83%) of pure **91** was obtained after passing through a short column of silica gel. The formation of tertiary amine products which normally limits the use of one-step reductive alkylation methods was absent in the aforementioned case as the isopropyl moiety of the valine group prevents the reaction of the secondary amine with a further molecule of aldehyde **90**.

The remaining steps of the synthesis were carried out as described previously: Boc-deprotection of **91** readily afforded diamine **82** which was coupled with Boc-D-Tic(OH)-OH (**86**) to give **83**. Finally, treatment with trifluoroacetic acid afforded the required ligand **66**. Overall, the new synthetic route was found to be both faster to perform and experimentally more convenient than the purely linear approach. This will greatly facilitate larger scale synthesis if **66** is subsequently found to be of pharmacological significance.

CHAPTER 4

INVESTIGATION OF 3-AMINO ANALOGUES OF 2-AMINO-1,1-DIMETHYLTETRAHYDRONAPHTHALEN-7-OL

4.1 Design rationale

The investigations of Roy *et al.*[126] into the binding affinity and analgesic activity of 3-substituted aminotetralins constituted a range of analogues utilising various alkyl, oxygenated and sulfonated 3-substituents. As discussed in Chapter 3, it transpired that the more potent members of this series were terminal methyl derivatives resembling structure **64**; of particularly high μ affinity were the heteroatomic SCH_3 and OCH_3 analogues which possessed a *trans* orientation relative to the primary amine group.

The specific rationale which led to the introduction of heteroatomic 3-substituents in the Roy series of aminotetralins is not entirely clear, as the design of the ligands was apparently inspired by dezocine (**20**, p. 19) which possesses a purely alkyl 3-substituent. By comparing the structure of **64** with that of morphine (**1**), one might speculate that the 3-substituent is intended to mimic the bridging ring of the epoxymorphinans. The highlighted bonds of morphine (**1**) in Figure 15 illustrate the structural features common to both **1** and aminotetralin **64**; it can be clearly seen that the tertiary nitrogen centre of **1** and heteroatom "X" of **64** share equivalent positions.

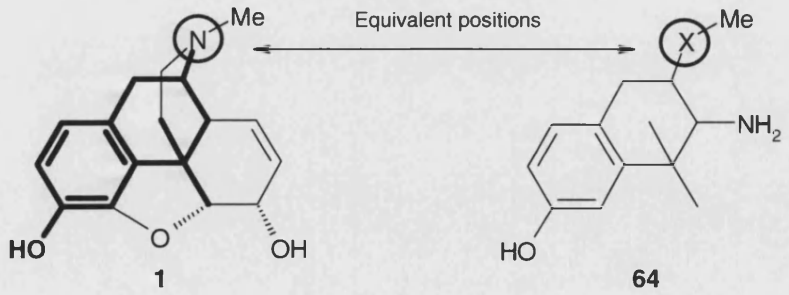


Figure 15 (Common structural features of **1** and **64**; equivalence of the tertiary nitrogen centre to the heteroatomic 3-substituent of **64** is apparent)

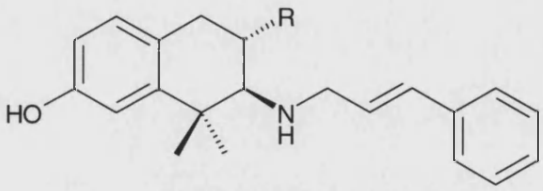
If mimicry of the bridging ring of **1** by the XCH_3 group of **64** is indeed occurring, it would be of interest to synthesise and biologically evaluate a series of analogues of **64** bearing nitrogenated 3-substituents. Given that a nitrogen centre in this position is common to all analgesic epoxymorphinans, it is somewhat surprising that the series of Roy *et al.*[126] had not been extended to include such derivatives (in view of the findings discussed in this chapter, it is possible that synthetic difficulties may have precluded prior investigation of these compounds).

It has been established that the tertiary nitrogen centre of the epoxymorphinans increases opioid receptor affinity by interacting electrostatically with the Asp138 residue common to all three opioid receptor types[24] (see Figure 3). Since the primary amine moieties of 2-aminotetralins **23** (p. 21) and **65** (p. 58) occupy a similar position (differing by only one carbon atom) with respect to the phenolic group, an equivalent electrostatic interaction would be expected to partially account for the observed opioid receptor affinity of these ligands. As illustrated in Figure 15, an amine moiety in the 3-position would closely mimic the bridging nitrogen group of morphine (**1**), perhaps placing it in a superior position for interaction with Asp138; the amine group at the 2-position would then act solely as a means to direct the 'address' side-chain towards its subsite on the receptor. The close proximity of the amine groups in such a series also suggests an alternative binding mode where both are suitably positioned for interaction with the Asp138 residue leading to the establishment of two electrostatic bonds; this too may have interesting repercussions for the pharmacological profile of the ligand.

As discussed in the previous chapter, the trend in binding affinity of the CH_2CH_3, OCH_3 and SCH_3 analogues of Roy *et al.*[126] implies that an electrostatic interaction is not responsible for the differences in K_i observed in this series. An analogous series of ligands bearing nitrogenated basic 3-substituents would not be expected to adopt a similar mode of binding to the existing compounds of structure **64** as the 3-substituent would be positively charged at physiological pH and able to interact with the receptor in the electrostatic manner described above. This makes such a series unique from the other 3-substituted analogues previously reported.

A rather different approach was taken to the design of the present series of nitrogenated 3-substituted ligands from that used in the oxygenated analogues described in Chapter 2. In the previous series, the 3-substituent universally employed was OCH_3 due to its previous reported success at enhancing opioid

receptor affinity. Diversity was then introduced by variation of the *N*-substituent in order to investigate the effect of different side-chains on receptor binding and selectivity. It was thought that an interesting alternative approach would be to retain the identical *N*-substituent at the 2-position throughout the series, but to vary instead the nitrogenated 3-substituent. Despite the high potency obtained by the use of OCH_3 and SCH_3 groups at the 3-position, it is somewhat surprising that Roy *et al.*[126] did not expand on these results by the investigation of other related 3-substituents (such as OCH_2CH_3) in order to determine whether such changes might lead to even greater receptor affinity. In view of this, it was decided to adopt such a 'reverse' approach to the design of the present series of nitrogenated 3-substituted ligands (**92-94**). The results will provide additional insight into the effect of the 3-substituent on opioid receptor binding and assist in determining whether other 'non-methyl' oxygenated/sulfonated 3-substituents would also be worthy of investigation (though due to the possible differences in binding mode of the nitrogenated analogues **92-94**, equivalent pharmacological profiles may not be obtained in the oxygenated/sulfonated series).



92: R = 

93: R = 

94: R = HNMe

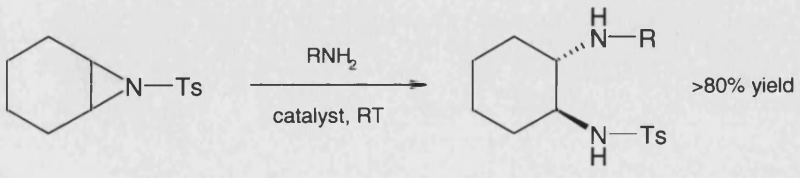
It was disclosed in Chapter 1 that the analogue which exhibited highest opioid receptor binding in the preliminary series derived from scaffold **23** was the *N*-cinnamyl derivative (**26**, p. 24). Such cinnamyl substituents are readily introduced by facile reductive alkylation and it was thus decided to retain this *N*-substituent throughout the present series and observe the effect of varying the 3-substituent on receptor binding.

The pyrrolidine analogue (**92**) was selected for investigation for three reasons: i) a pyrrolidine moiety is present in many of the arylacetamide series of κ selective agonists from which the κ selective antagonists UPHIT (**16**, p. 18) and DIPPA are directly derived and is the sole basic nitrogen centre in both, strongly suggesting that interaction with the Asp138 residue occurs as described above (this

mode of interaction has indeed been proposed for the arylacetamide U50488 κ agonist[24]); ii) the evaluation of ligands containing strongly basic tertiary nitrogen centres at the 3-position will assist in determining whether interaction with an anionic residue in the receptor is occurring; iii) tertiary amine centres are less susceptible to electrophilic attack than secondary amines and therefore would not require protecting during the synthesis – this makes pyrrolidine a better choice of 3-substituent for initial testing of the chemistry than, for example, NCH_3. The *N*-cyclopropylmethyl analogue (**93**) was proposed on the basis of this group being associated with antagonist behaviour in the epoxymorphinan series, *e.g.* naltrexone (**8**); the frequent appearance of this group in opioid ligands made it a logical choice for investigation. Finally, the *N*-methyl derivative (**94**) would enable direct comparison to the OCH_3 derivative (**74**, p. 70) whose synthesis was described in Chapter 3.

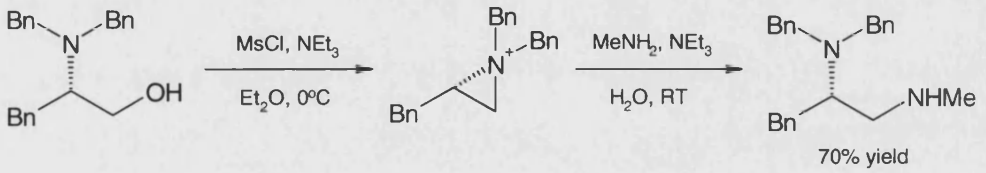
4.2 Literature methods of *trans* vicinal diamine synthesis

Although there is no specific literature precedent for the synthesis of *trans* vicinal diamines of an aminotetralin-like structure, two general approaches to this functional group have been developed. The ring-opening of aziridines with amine nucleophiles constitutes the first and most widely investigated method for *trans* vicinal diamine synthesis. A whole plethora of catalysts have been developed in recent years specifically to promote ring-cleavage of activated aziridines with primary and secondary amines, including bismuth trichloride[151], lithium bistrifluoromethanesulfonimidate[143] and ytterbium (III) triflate[152]. High yields of the corresponding protected diamines are obtained under mild conditions (Scheme 29), and recycling of the catalyst is often possible.



Scheme 29 (Synthesis of *trans* vicinal diamines by catalysed ring-opening of aziridines)

A rather interesting alternative approach to the synthesis of vicinal diamines uses an aziridinium ion to introduce the required *trans* stereochemistry[153,154] (Scheme 30). Tertiary amino-alcohols (obtained from the corresponding epoxides) are treated with methanesulfonyl chloride in the presence of excess triethylamine to give the highly reactive mesylate species; subsequent intramolecular nucleophilic attack by the tertiary nitrogen results in ring-closure and formation of an aziridinium ion. The desired primary or secondary amine nucleophile is then introduced which attacks the strained intermediate at the least hindered carbon resulting in ring-opening in an analogous manner to aziridines: *trans* stereochemistry is likewise always observed. This method appeared attractive as it uses inexpensive and relatively environmentally-friendly reagents; one noticeable disadvantage, however, is that the reacting amine centre must be tertiary which in turn may necessitate additional synthetic steps. Given that aziridine ring-opening chemistry had previously been employed successfully for the synthesis of the 3-methoxy analogues and that a reliable route to intermediate aziridine **68** (Scheme 22) had previously been established, it was decided to initially adopt the former approach (*i.e.* Scheme 29) to the synthesis of ligands **92-94**.



Scheme 30 (Synthesis of *trans* vicinal diamines using an aziridinium intermediate[153])

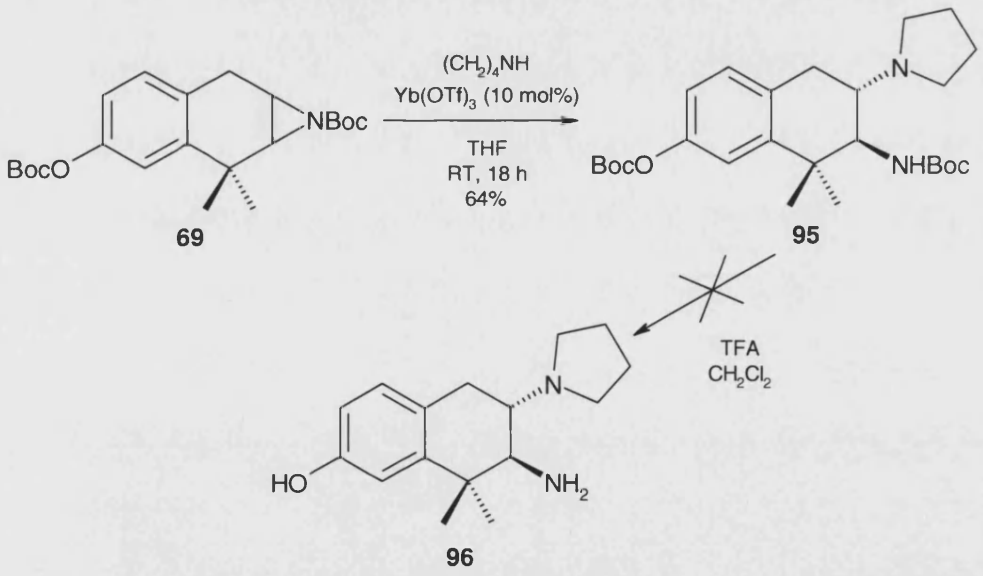
4.3 Preliminary synthetic studies

4.3.1 Ring-opening of aziridines bearing carbamate activating groups

Di-Boc protected aziridine **69** was the universal intermediate for all 3-substituted analogues reported by Roy *et al.*[126] and appeared a logical starting point for the synthesis of the present *trans* vicinal diamines. It was initially envisaged that a two-step route (Scheme 31) involving ring-opening of **69** with pyrrolidine in the presence of an appropriate catalyst would afford protected diamine **95**; subsequent Boc-deprotection would afford the aminotetralin **96** which could be furnished with a

cinnamyl *N*-substituent using the stepwise reductive alkylation protocol previously described.

Of the many available catalysts which have been developed to effect aziridine ring-cleavage with amine nucleophiles, the lanthanide Lewis acid ytterbium (III) trifluoromethanesulfonate appeared particularly appropriate for this purpose. Meguro and Yamamoto[152] report that ring-opening of aziridines proceeds with high yield and regioselectivity with this compound to give masked *trans* vicinal diamines under mild conditions. One of the major deciding factors for the use of this catalyst in the present investigation is its reported compatibility with Boc as the aziridine activating group. Additional advantages of $Yb(OTf)_3$ include low catalyst loadings (typically 10 mol% is required), insensitivity to moisture and low cost. Activated aziridine **69** was therefore treated with 10 mol% $Yb(OTf)_3$ and pyrrolidine in THF at room temperature, affording a 64% yield of protected diamine **95** after column chromatography. TLC analysis of the reaction mixture showed no trace of the other regioisomer.



Scheme 31 (Attempted synthesis of diamine **96** by cleavage of Boc-activated aziridine **69**)

It was expected that Boc-deprotection of **95** would proceed smoothly to afford the free base **96** which could be subsequently converted to ligand **92** by reductive alkylation. However, treatment of **95** with trifluoroacetic acid in the standard manner was found to result in complete decomposition when the crude

reaction mixture was examined by TLC; repetition of the reaction using fresh trifluoroacetic acid gave an identical outcome. Although difficulties in the cleavage of Boc groups are relatively uncommon except in cases where the substrate is particularly acid sensitive, such decompositions of Boc-protected diamines have been reported.[155] It is possible the problem was caused by highly reactive *tert*-butyl trifluoroacetate liberated during the Boc-deprotection process which subsequently undergoes further reaction with the substrate; the phenolic moiety of tyrosine analogues has been reported to undergo undesirible reactions of this nature.[156]

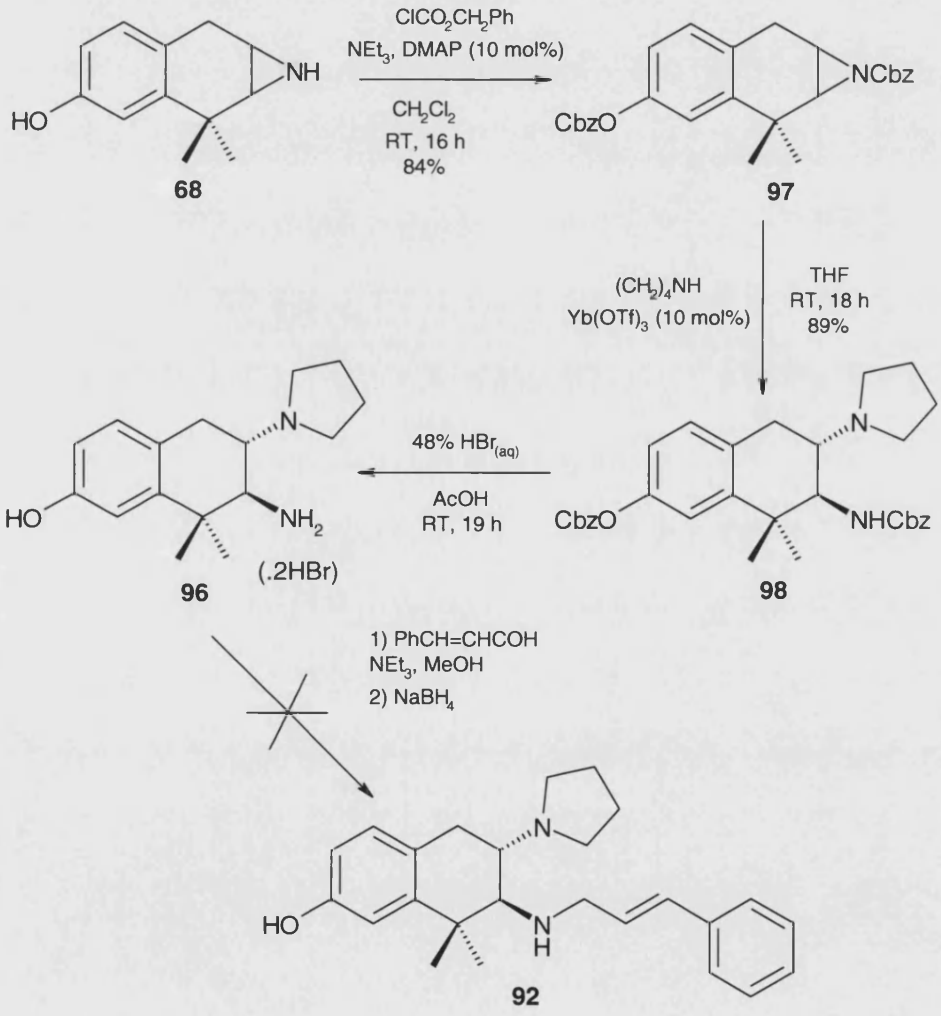
The carbobenzoxy (Cbz) amine protecting group is a carbamic acid derivative closely related to Boc which undergoes a similar mechanism of deprotection in the presence of strong protic acids. Although the conditions required to cleave the Cbz group are harsher than for Boc, it possesses a distinct advantage for the present investigation in that deprotection liberates the somewhat less reactive benzyl bromide; the difficulties thought to arise from the presence of *tert*-butyl trifluoroacetate during Boc cleavage may thus be avoided. It was therefore decided to re-attempt the synthesis of **96** using Cbz as the activating group (Scheme 32).

Preparation of the activated aziridine **97** was achieved by treating previous intermediate **68** with benzyl chloroformate in the presence of excess triethylamine and the acylation catalyst DMAP. The reaction proceeded smoothly and a high yield of **97** was obtained after simple column chromatography. Although Meguro and Yamamoto[152] do not report the use of $Yb(OTf)_3$ with Cbz as the activating group, the great similarity between the latter and Boc suggested that compatibility issues were unlikely. Hence di-Cbz protected aziridine **97** was reacted with pyrrolidine under analogous conditions to that used for **69**, resulting in a high (89%) yield of **98** after purification.

There are two major methods in the literature for the cleavage of Cbz groups: catalytic hydrogenation (typically Pd/C) and concentrated HBr in acetic acid.[156] The latter appeared to be the more convenient and averted possible complications resulting from chelation of palladium by the vicinal diamine group. Therefore, **98** was treated with a 1:1 mixture of 48% aq. HBr and glacial acetic acid at room temperature. TLC of the crude reaction mixture indicated the presence of several products, though one appeared to be present in greater quantity than the others. Evaporation of the solvent afforded a quantitative yield of the di-HBr salt, but

attempted isolation of the free base *via* treatment with excess concentrated ammonia and extraction resulted in a very low (<20%) recovery.

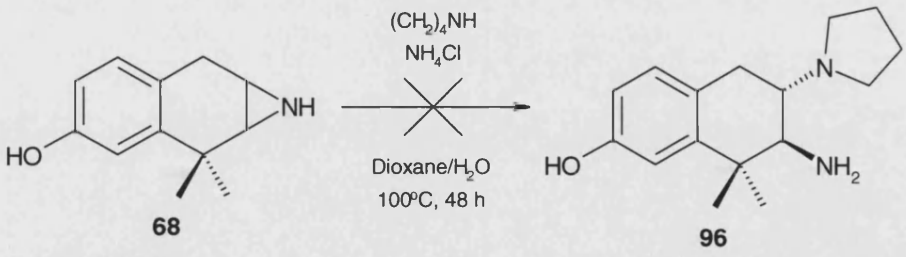
The isolated free base of **96** was subsequently found to be virtually insoluble in CH_2Cl_2 and $CHCl_3$, probably accounting for the poor recovery of crude product. The ^1H NMR spectrum suggested the major product was the desired **96** but the sample contained significant impurities; recrystallisation from propan-1-ol/diethyl ether afforded a degree of improvement but with an approximately 40% loss of material.



Scheme 32 (Modified synthesis of diamine **96** and attempted conversion to ligand **92**)

Due to the aforementioned difficulties with obtaining sufficient quantities of the free base of **96**, it was decided to attempt reductive alkylation with *trans*-cinnamaldehyde by forming the free base *in situ*; this method has been reported by Abdel-Magid and co-workers[120] using triethylamine as the base. The di-HBr salt of **96** was therefore reacted with 1.5 equivalents of *trans*-cinnamaldehyde and 4 equivalents of triethylamine in MeOH. After stirring for 24 hours at room temperature, the mixture was treated with excess sodium borohydride. Unfortunately, the TLC of the resulting crude product revealed the presence of several products, none of which were conclusively identified as the desired **92** after column chromatography.

A final attempt at producing diamine intermediate **96** was made which involved the direct ring-cleavage of **68** (Scheme 33). Although it was stated in Chapter 3 that the products of *N*-unsubstituted aziridine ring-opening readily undergo oligomerisation, the successful cleavage of a simple *N*-unsubstituted cyclohexyl-aziridine with pyrrolidine has been reported by Cheng *et al.*[157] utilising ammonium chloride as catalyst. The reaction was carried out in dioxane/water with prolonged heating at 100°C; the necessity of such harsh conditions serves to illustrate the powerful effect on reactivity exerted by activating *N*-substituents. Treatment of aziridine **68** under identical conditions afforded only decomposition, however, and this route was consequently abandoned.



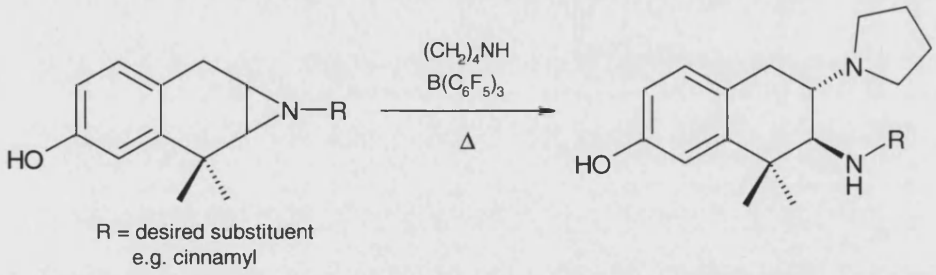
Scheme 33 (Attempted direct ring-cleavage of **68**)

To summarise, it appeared that the simple ring-opening/deprotection strategy which was successfully applied to the synthesis of 3-methoxyaminotetralin **65** would not be a viable approach for the present diamine series. The difficulties associated with the isolation of the free base of **96** and its lack of organic solubility made purification and subsequent introduction of the side-chain somewhat troublesome.

After consideration of these issues, it was decided to investigate the use of alternative synthetic routes which did not incorporate **96** as an intermediate.

4.3.2 Ring-opening of aziridines bearing unactivated N-substituents

In 2003, Watson and Yudin[158] disclosed a study which reported the efficacy of tris(pentafluorophenyl)borane as a catalyst specifically for the ring-opening of nonactivated aziridines with amine nucleophiles. This study was unique in its focus on nonactivated aziridine *N*-substituents – previous studies of catalytic aziridine ring-cleavage almost invariably focused on strongly activating *N*-substituents which effect ring-opening under far milder conditions. It therefore appeared that a possible approach to the required vicinal diamine ligands might be alkylation of the aziridine nitrogen with the *N*-substituent required to be at the 2-position (cinnamyl in the case of **92-94**), followed by $B(C_6F_5)_3$-assisted ring-opening with the primary or secondary amine required to be at the 3-position (Scheme 34). Unlike the synthetic approaches to **92-94** discussed in Section 4.3.1, this route does not incorporate the problematic intermediate diamine **96** or rely on reductive alkylation to introduce the side-chain (thus eliminating the need to protect the 3-substituent when the aziridine is cleaved with primary amines).

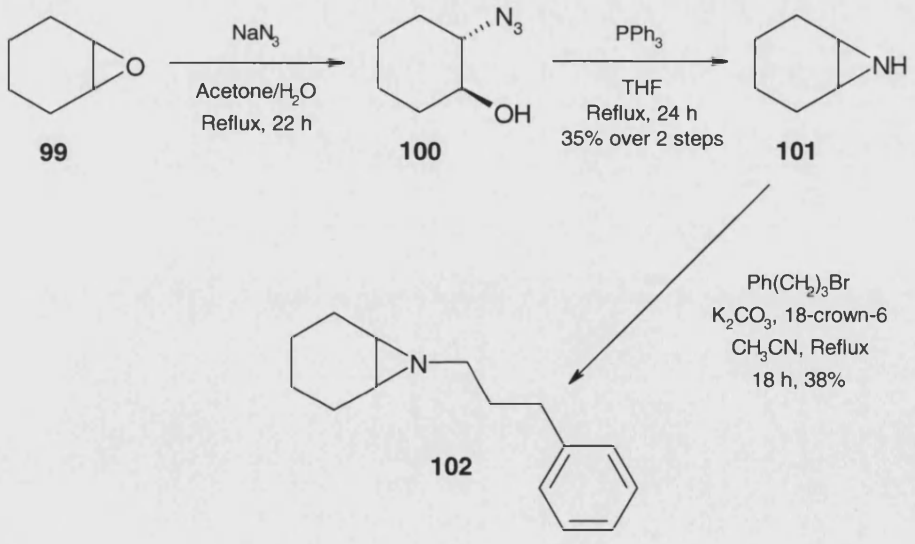


Scheme 34 (Proposed ring-opening of unactivated *N*-alkyl aziridines)

One of the major priorities in the development of a synthetic route to the present series of ligands was the ability to introduce a variety of primary and secondary amines to the 3-position; the option to use side-chains other than cinnamyl is also highly desirable (and will be a necessity if the pharmacological results of this preliminary series appear promising). Whilst Watson and Yudin comprehensively investigated the mechanism and conditions of B(C6F5)3-assisted ring-cleavage[158], the actual range of *N*-substituents and amine nucleophiles tested was rather limited.

Not wishing to waste valuable material, it was decided to further investigate the scope of the reaction by initially utilising a simplified and rapidly accessible model compound. Watson and Yudin[158] thoroughly investigated the ring-opening of *N*-benzyl substituted aziridines with $B(C_6F_5)_3$ and report universally high yields (84-99%); non-benzylic unactivating N-substituents, however, afforded mixed results and the range of examples is very limited. For this reason, it was decided to incorporate a 3-phenylpropyl *N*-substituent into the model compound (**102**) rather than a cinnamyl substituent, as it was thought that the latter would resemble benzyl in reactivity; the results obtained using a 3-propylphenyl *N*-substituent are therefore likely to be a better reflection of the true scope of the reaction.

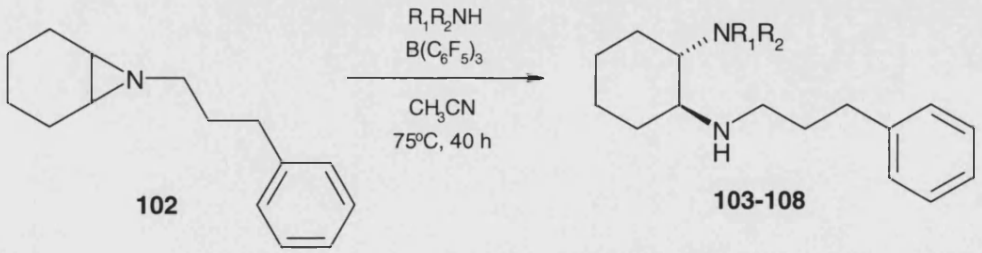
Scheme 35 illustrates the synthetic route used to obtain the cyclohexane-based model compound, **102**. The intermediate aziridine **101** was prepared according to a literature procedure.[157] Thus, cyclohexene oxide (**99**) was reacted with sodium azide under reflux conditions to afford *trans*-azidoalcohol **100**. Ring-closure in the presence of triphenylphosphine in a variation of the Staudinger reaction gave **101** in 35% overall yield; a low recovery of product after vacuum distillation of the crude aziridine most likely accounts for the poor yield.



Scheme 35 (Synthetic route used to prepare model compound **102**)

Alkylation of **101** with 1-bromo-3-phenylpropane was initially attempted using sodium hydride in refluxing THF, although only a 25% yield of *N*-substituted aziridine **102** was obtained after column chromatography. An alternative protocol developed specifically for the *N*-alkylation of aziridines has been described by Åhman *et al.*[159] utilising potassium carbonate and catalytic 18-crown-6 in THF. These milder conditions are reported to afford yields of the *N*-alkylated products which are far superior than those obtained using sodium hydride. Treatment of **101** with 1.2 equivalents of 1-bromo-3-phenylpropane according to the literature protocol resulted in only a trace of product being visible by TLC after 15 hours at room temperature. Heating the system to reflux for 18 hours afforded a 38% yield of the required compound **102** after purification, but the recovery of a significant quantity of the bromide indicated that complete conversion had not occurred (reflecting the low reactivity of the electrophile). Aside from this, the TLC showed the reaction to be very clean and doubtless the yield could be much improved upon after prolonged reflux.

Ring-opening of **102** was then attempted using a range of amine nucleophiles according to the protocol of Watson and Yudin.[158] Thus, 1 equivalent of aziridine **102** was treated with 1.2 or 4.0 equivalents of the nucleophile (according to its expected reactivity) and 10-20 mol% of $B(C_6F_5)_3$ in non-anhydrous acetonitrile (see below). The system was heated at 75°C for 40 hours without any precautions to exclude moisture, after which time the crude product was stirred with Amberlyst A-21 ion exchange resin to remove the catalyst. Purification was achieved by column chromatography affording the yields quoted in Table 11. All amine nucleophiles were obtained commercially, with the exception of **109** which was synthesised in 88% yield by the stepwise reductive alkylation of aminomethylcyclopropane with benzaldehyde.



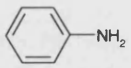
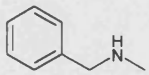
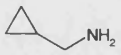
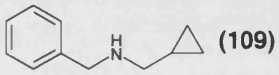
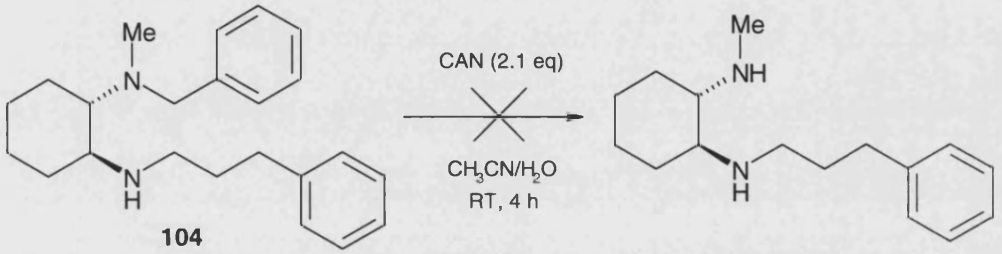
No	Nucleophile	Eq. of Nuc.	Mol% $B(C_6F_5)_3$	Yield
103		1.2	10	100%
104		4.0	20	63%
105		4.0	20	0%
106		4.0	20	0%
107	 **(109)**	4.0	20	0%
108		1.2	10	65%

Table 11 (Attempted ring-opening of aziridine **102** with amines in the presence of $B(C_6F_5)_3$)

Aziridine **102** was found to undergo efficient ring-cleavage in the presence of aniline to afford **103** in quantitative yield - this is consistent with the high yields obtained with this nucleophile by Watson and Yudin.[158] *N*-Methylbenzylamine also afforded a satisfactory yield of the corresponding diamine **104**. The use of a masked methylamine derivative was considered to be more appropriate than methylamine itself in this case, as the prolonged heating required to effect ring-opening would inevitably result in substantial loss of the nucleophile from the reaction mixture. For this approach to be viable for the synthesis of 3-aminomethyl substituted ligands, a satisfactory cleavage method for the tertiary *N*-benzyl group was required. Although catalytic hydrogenation is normally the preferred technique for *N*-debenzylation[97], this method would preclude the use of unsaturated side-chains (such as cinnamyl) at the 2-position and therefore restrict the range of ligands which could be prepared using this synthetic route. An alternative method which utilises ceric ammonium nitrate (CAN) to selectively cleave tertiary *N*-benzyl groups has been reported by Bull and co-workers.[160] The reaction proceeds *via* an oxidative cleavage mechanism and high yields of the corresponding secondary amines are reported for many substrates under mild conditions. This technique appeared attractive for the present

investigation as functionalities normally sensitive to catalytic hydrogenation are reported to remain unaffected in the presence of CAN; however, treatment of **104** under the conditions specified resulted only in decomposition of the substrate (Scheme 36) and it was consequently decided not to pursue this method further although the $B(C_6F_5)_3$-catalysed approach to 3-aminomethyl derivatives may yet prove to be of use where a saturated side-chain is desired at the 2-position (*i.e.* one which would remain unaffected by hydrogenative debenzylation).



Scheme 36 (Failed cleavage of tertiary *N*-benzyl group with ceric ammonium nitrate)

Ring-cleavage using pyrrolidine, aminomethylcyclopropane or nucleophile **109** was not previously reported by Watson and Yudin.[158] Unfortunately, none of these amines were found to afford any degree of reaction with aziridine **102** even when large excesses of the nucleophile were used. A possible explanation may lie with the mechanism of $B(C_6F_5)_3$-activated ring-opening. Through substantial NMR investigations, the original authors of the method have concluded that the *in situ* formed $[(C_6F_5)_3B(OH_2)].H_2O$ is the species which most likely catalyses aziridine ring-opening. The complex has been shown to exert its effects *via* a Brønsted acid mechanism involving protonation of the aziridine nitrogen to form an activated aziridinium ion which subsequently undergoes attack by amine nucleophiles. The probable intermediate species formed between the $[(C_6F_5)_3B(OH_2)].H_2O$ complex and **102** is illustrated in Figure 16.

The Brønsted acid mechanism described above implies that the ability of the catalyst to activate the aziridine depends on the attacking amine nucleophile being of lower pKa than the aziridine nitrogen. If this is not the case and the amine is of significantly higher basicity than the substrate, then the expected pathway of the reaction would be protonation of the amine and consequent inhibition of ring-

opening. Table 12 lists the pKa values for amine nucleophiles tested for use with $B(C_6F_5)_3$. A noticeable decrease in ring-opening efficacy is apparent when the pKa of the attacking amine increases beyond that of benzylamine. Sweeney[127] gives the pKa of unsubtituted aziridine (*i.e.* C_2H_4NH) as being 7.98, though it is likely that the value will be higher in the case of substituted **102**. It is possible then that benzylamine represents the uppermost limit of pKa for $B(C_6F_5)_3$-mediated ring-cleavage of **102**, with more basic amines such as *n*-butylamine (and aminomethylcyclopropane) completely inhibiting protonation of the aziridine nitrogen.

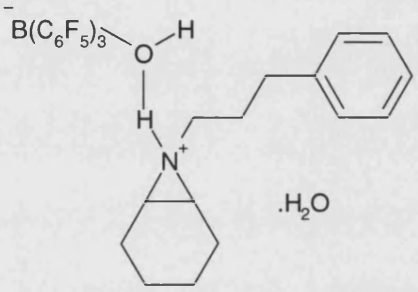


Figure 16 (Activated aziridinium complex formed between $[(C_6F_5)_3B(OH_2)].H_2O$ and **102**)

Amine	pKa[161]	Outcome of reaction*
Aniline	4.63	High (>95%) yields
Benzylamine	9.33	High (>95%) yields
t-Butylamine	10.68	Did not go to completion with excess NuH
n-Butylamine	10.77	Long rxn times and large excess of NuH needed
Pyrrolidine	11.27	No reaction

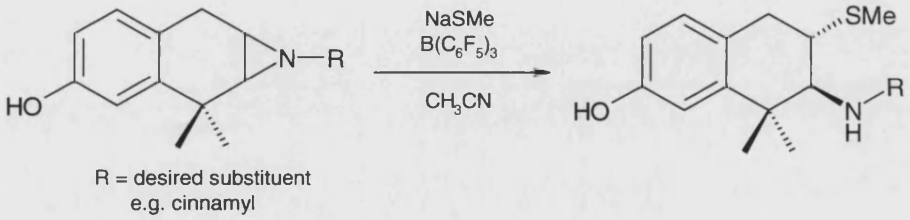
*Combined findings of current investigation and Watson & Yudin[158]

Table 12 (pKa values of amine nucleophiles and corresponding reactivity)

Additional evidence for the above hypothesis is provided by Watson and Yudin[158], who report that addition of Proton Sponge (pKa 12.1) to the reaction mixture severely retards ring-cleavage. In the case of *t*-butylamine and nucleophile **109**, steric hindrance would also be expected to contribute significantly to the observed lack of reactivity. Due to the poor results obtained from attempted ring-

opening of model compound **102**, it was decided not to further investigate the use of an unactivated aziridine pathway to synthesise ligands **92-94**.

On a final note, Watson and Yudin[158] report that benzenethiol is superior to amine nucleophiles in effecting ring-opening with $B(C_6F_5)_3$. This is to be expected, as thiols possess both higher nucleophilicity and lower basicity than amines. As benzenethiol was the only sulfonated nucleophile tested, it was of interest to see if the reaction could be applied to alkyl thiols as well as aromatic thiols. Reaction of 1-propanethiol with **102** afforded a 65% yield of the corresponding ring-opened product after only 2 hours at room temperature. Aziridine ring-opening with thiols using this protocol might therefore provide a considerably shorter synthetic route to ligands bearing sulfonated 3-substituents than the approach used by Roy *et al.*[126] as the required compounds could be obtained directly from the *N*-alkyl aziridines (*e.g.* Scheme 37).



Scheme 37 (Application of $B(C_6F_5)_3$ to the synthesis of sulfonated 3-substituted aminotetralins)

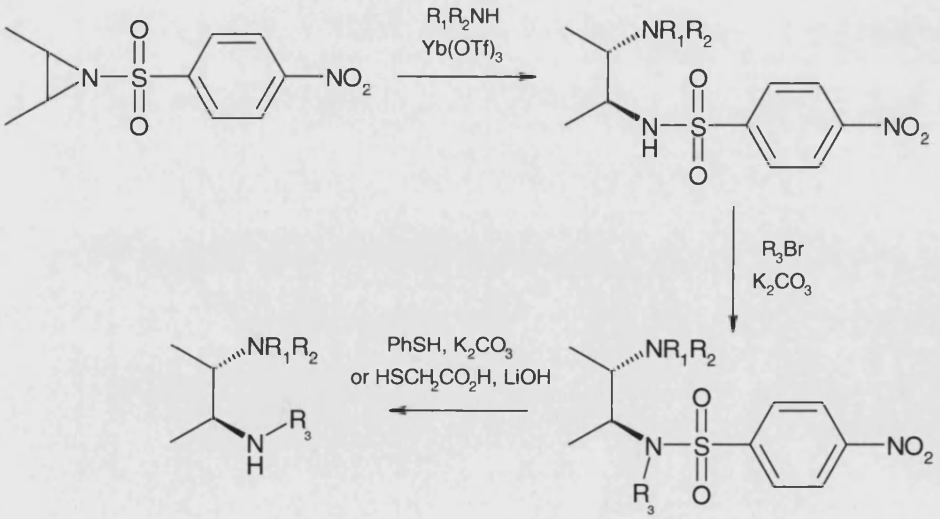
4.4 Synthetic studies using the nosyl protecting group

4.4.1 Overview and rationale

Of the two approaches to *trans* vicinal diamines investigated in Section 4.3, it appeared that ring-opening of activated aziridines was the more promising of the two routes; however, significant difficulties were associated with the isolation and purification of the polar 2-unsubstituted diamine intermediate **96** (Scheme 31) which prevented the final reductive alkylation step in the synthesis. A synthetic strategy was therefore required which did not incorporate such an intermediate. It was thought that if the desired side-chain could be installed whilst the amine moiety at the 2-position was masked as an amide, carbamate or sulfonamide then the molecule would be less polar, more soluble in organic solvents and therefore easier to purify than **96**. Deprotection to afford the vicinal diamine would preferably be the last step

of the synthesis, allowing the final ligand to be purified by recrystallisation of the salt if solubility problems were apparent (though the lipophilicity of the side-chain should increase organic solubility).

An extensive search of the literature revealed a protecting group which appeared to satisfy the above criteria. The nitrobenzenesulfonyl (nosyl) group was used by Fukuyama *et al.*[162] as a facile means of preparing and protecting secondary amines. Reaction of a primary amine with 2- or 4-nitrobenzenesulfonyl chloride in the presence of triethylamine gives the corresponding secondary sulfonamide. Due to the electron-withdrawing effect of the nitro group, the sulfonamide proton is significantly acidic and may be removed with relatively weak bases such as potassium carbonate. This enables alkylation to be performed under mild conditions (far milder than carbamate derivatives, for instance, which require sodium hydride to deprotonate them). The nosyl group may then be selectively cleaved using thiolates (typically benzenethiol/K_2CO_3 or mercaptoacetic acid/LiOH) to afford the required secondary amine. The non-acidic conditions of the deprotection stage make this group particular attractive as it averts possible complications in the reaction work-up arising from protonation of the diamine. A proposed general synthetic strategy (when R_1R_2N is a tertiary amine) is illustrated in Scheme 38.



Scheme 38 (The nosyl group as applied to the synthesis of *trans* vicinal diamines)

The nosyl group has also been reported to be a highly activating *N*-substituent for aziridines[163], being 50-60 times more activating than the tosyl group and is compatible with a wide range of nucleophiles. Overall, the nosyl group appeared to be the ideal activating group for the present project and it was decided to further investigate its potential application in the synthesis of the desired series of diamine ligands.

4.4.2 Synthesis of model compounds

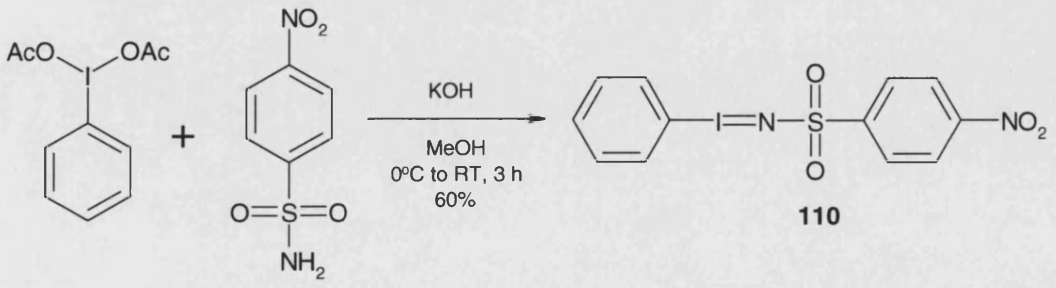
In order to test the feasibility of the proposed nosyl approach to diamines (Scheme 38), it was decided to prepare a model compound analogous to aziridine **102** (p. 90) on which to first test the synthetic route (Scheme 39). One particular motivation for such an approach was to gain an understanding of the stability and solubility of the final diamines, in particular to determine whether purification may be carried out by the preferred method of column chromatography rather than by recrystallisation of the HCl salt. This knowledge would be invaluable when applying the chemistry to the synthesis of the corresponding aminotetralin ligands as loss of material at the final stage of the synthesis could be prevented.

It appeared logical to retain the simple cyclohexyl-aziridine structure incorporated into **102** due to the synthetic accessibility of such compounds. It was initially envisaged that the equivalent nosyl aziridine would be most easily prepared by sulfonation of aziridine **101** (prepared in two steps from cyclohexene oxide) with nitrobenzenesulfonyl chloride. However, review of the literature revealed that nosyl aziridines may be prepared directly from alkenes by the catalytic addition of a suitable nitrene species.[127,130,164,165]

The increasing realisation of the number of potential applications for aziridines in organic synthesis has generated considerable interest in the development of efficient methods for the one-step aziridination of alkenes. The mechanism of aziridination is invariably nitrene addition to the double bond[127], and a variety of nitrene precursors have been investigated for their ability to undergo addition in an efficient manner. The use of alkoxycarbonylnitrenes and azides for this purpose is well established in the literature, but generation of the active nitrene species generally requires photolysis or heating.[166] More recent research has focused on the use of metal-stabilised nitrenes as aziridinating agents, of which *N*-tosyliminophenyliodinane and its derivatives have attracted particular attention in

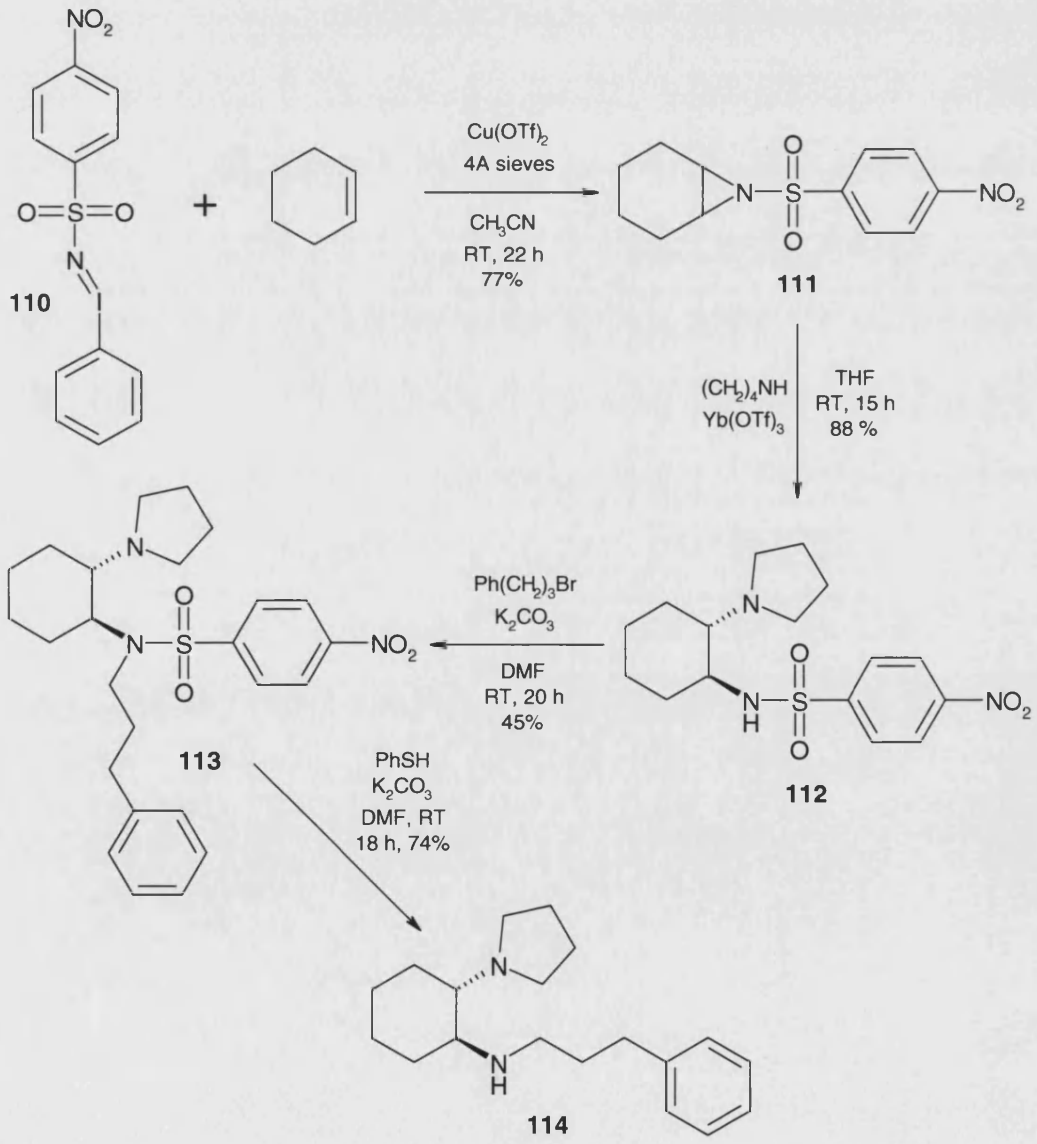
this regard. The first successful reported aziridination using this nitrene precursor was reported in 1984 by Mansuy *et al.*[167] who utilised Fe(III) and Mn(III) porphyrins as catalysts. Since then, interest has shifted towards Cu(I) and Cu(II)-based catalysts which are more accessible and often afford very high yields of the corresponding aziridines.[130,164]

The preparation of model compound **111** from cyclohexene has been reported to proceed in 92% yield in the presence of catalytic $[Cu(CH_3CN)_4]ClO_4$ and the nitro analogue (**110**) of *N*-tosyliminophenyliodinane[164] (conveniently for the present investigation, nitrene precursor **110** has been consistently reported to undergo addition to alkenes in higher yields than the parent *N*-tosyliminophenyliodinane). However, this particular copper catalyst did not appear to be readily commercially available and attention turned instead to the use of copper (II) trifluoromethanesulfonate. This catalyst has been studied in great detail by Taylor *et al.*[130] in conjunction with the aziridination of styrene by the aforementioned nitrene precursors and is relatively inexpensive. As the synthesis of the corresponding tosyl analogue of **111** using $Cu(OTf)_2$ had been previously reported in 68% yield[168], it therefore appeared extremely likely that nitrene precursor **110** would react with similar (or greater) efficacy given its established superior ability as an aziridinating agent. The preparation of **110** was carried out according to the very convenient one-step procedure of Taylor *et al.*[130] (Scheme 39). Thus, equimolar quantities of hypervalent iodobenzene diacetate and *p*-nitrobenzenesulfonamide were combined in methanolic potassium hydroxide solution. After stirring for 3 hours, the required **110** was isolated in 60% yield (consistent with the literature value) by simple suction filtration of the reaction mixture.



Scheme 39 (Preparation of nitrene precursor **110**)

Cyclohexene was hence treated with 1.5 equivalents of nitrene precursor **110** and a catalytic amount of $Cu(OTf)_2$ in acetonitrile at room temperature (Scheme 40). The addition of **110** was carried out portionwise as Södergren *et al.*[164] report that slow addition of the nitrene precursor results in a superior yield. Column chromatography of the crude product obtained after 4 hours of stirring afforded a 77% yield of **111**, noticeably greater than the 68% yield reported with *N*-tosyliminophenyliodinane. It therefore appeared that direct nitrene transfer with **110** was indeed an excellent and convenient method for the synthesis of nosyl aziridine **111**.



Scheme 40 (Synthesis of model compound **111** and subsequent conversion to diamine **114**)

Due to the success of $Yb(OTf)_3$ in effecting aziridine ring-opening with amine nucleophiles observed in Section 4.3.1, it was decided to retain this catalyst for the present investigation. Treatment of **111** with pyrrolidine in the presence of $Yb(OTf)_3$ resulted in an 88% yield of masked *trans*-diamine **112** after passing the crude product through a short column of silica gel. Since nosyl *N*-substituted aziridines are reported to be very highly activated towards ring-opening, it was not known whether $Yb(OTf)_3$ actually improved the efficiency of the reaction by any measurable degree in this instance; however, it has since been shown that not all nosyl *N*-substituted aziridines are nearly so activated (see Section 4.4.3).

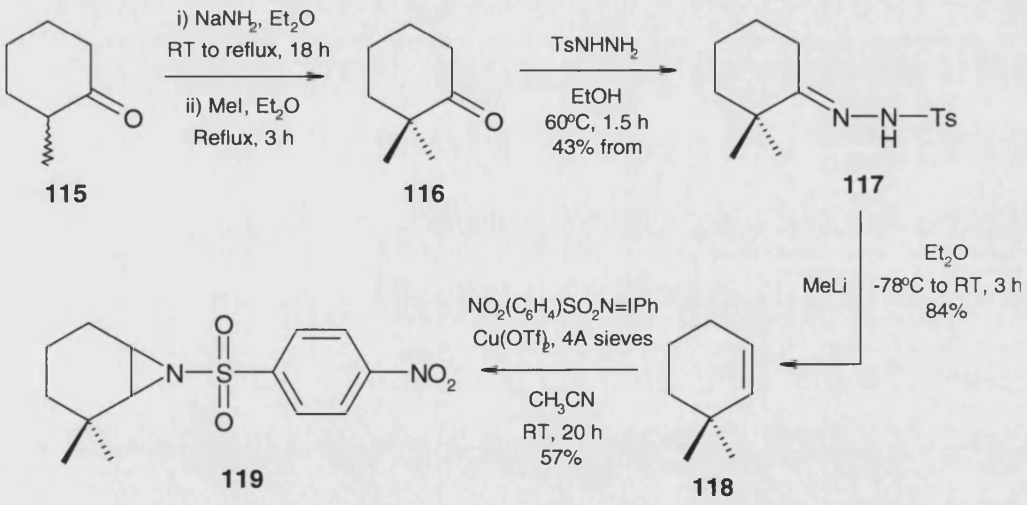
Alkylation of the secondary sulfonamide moiety of **112** was carried out according to the general literature procedure[162] employing 1.2 equivalents of 1-bromo-3-phenylpropane and excess potassium carbonate in DMF. A rather low yield (45%) of the tertiary sulfonamide **113** was obtained after 20 hours at room temperature; the isolation of a significant mass of unreacted 1-bromo-3-phenylpropane was indicative of the bromide's low reactivity (unreacted **112** was present as its potassium salt and therefore was not isolated during column chromatography). Higher yields would probably be obtained after prolonged stirring or heating of the system.

Of the two deprotection methods specified by Fukuyama *et al.*[162], the benzenethiol/K_2CO_3 system was selected due to the ready availability of the reagents. The addition of benzenethiol to excess potassium carbonate in DMF generates the benzenethiolate anion which efficiently cleaves nosyl groups *via* formation of a Meisenheimer complex with the substrate. Treatment of **113** with this reagent immediately resulted in a dark brown reaction mixture which was allowed to stir overnight. TLC analysis indicated the presence of 4 substances, of which one may be attributed to the by-product derived from reaction of the thiolate anion with the nosyl group. Separation by column chromatography and subsequent ^1H NMR analysis revealed that the most polar component corresponded to the desired *trans* vicinal diamine **114** which was obtained in 74% yield. A particularly pleasing finding was that no evidence of decomposition of **114** was apparent during chromatography which greatly simplified the purification.

The successful synthesis of diamine **114** using the nosyl strategy described above was highly encouraging and it appeared likely that this synthetic approach

would be applicable to ligands **92-94** (p. 82). The geminal dimethyl group of the previously synthesised aminotetralins has been shown on numerous occasions to impart steric hindrance to the 2-position. A remaining concern was whether the presence of the geminal dimethyl group would significantly attenuate alkylation of the secondary sulfonamide moiety and consequently render this synthetic route unusable for the preparation of **92-94**.

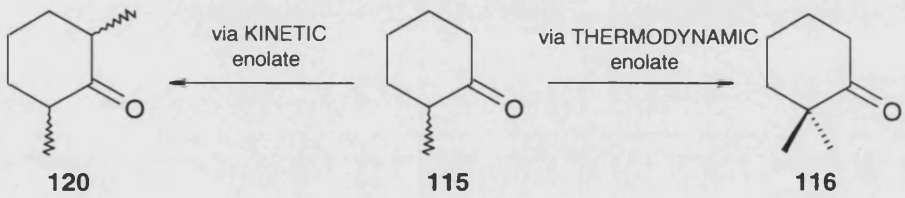
It was therefore decided to prepare a second model compound analogous to **111** with the addition of a geminal dimethyl group adjacent to the aziridine in order to further gauge the applicability of this synthetic strategy (**119**, Scheme 41). Such a *gem*-dimethylcyclohexane structure could also be considered as the 'next stage' in simplification of the aminotetralin scaffold, perhaps providing scope for a future series of ligands - this would enable the effect of the phenolic group on opioid receptor binding to be determined and hence discover to what extent the scaffold can be simplified before significant loss of opioid receptor affinity occurred.



Scheme 41 (Synthetic route used for synthesis of model compound **119**)

It appeared that introduction of the geminal dimethyl group by alkylation would be most appropriately carried out at an early stage of the synthesis, as such reactions often lead to substantial loss of material *via* alkylation of other positions in the molecule. Analysis of the literature showed that 2-methylcyclohexanone (**115**) may be methylated under suitable conditions to furnish 2,2-dimethylcyclohexanone[169] (**116**) (it should be noted that **116** is available

commercially but is extremely expensive). It was discussed in Chapter 2 that alkylation at the 1-position is strongly favoured in 2-tetralone **35** due to conjugation of the corresponding enolate with the neighbouring aromatic ring. Unfortunately, no such stabilisation occurs when **115** is deprotonated and consequently even more care must be taken over the reaction conditions to ensure that the desired *gem*-dimethyl product (**116**) is the major one. The enolate derived from **115** is a classic example of 'thermodynamic vs kinetic' reaction pathways. Deprotonation can occur at either the 2- or 6-positions of **115** leading to products **116** and **120** respectively (Scheme 42). Generation of the kinetic enolate is favoured by sterically hindered bases (attenuating deprotonation at the more hindered 2-position) and low temperatures (preventing isomerisation to the thermodynamic enolate). Accordingly, formation of the thermodynamic enolate is favoured by non-bulky bases and high temperatures.



Scheme 42 (Products of kinetic and thermodynamic enolates of **115**)

The base selected for use in the methylation of **115** was sodium amide (the compact nature of the anion should render hindrance from the 2-methyl group negligible) and the procedure adopted was a modified version of that described by Gärtner.[169] The thermodynamic enolate of **115** was generated by slow addition of the ketone to a suspension of sodium amide in diethyl ether, followed by prolonged stirring at room temperature and a subsequent period at reflux. Introduction of the electrophile and further reflux completed the reaction. Analysis of the methyl peaks in the ^{1}H NMR spectrum of the crude reaction mixture indicated that approximately 50% of the material was the desired compound **116**, with the remaining 50% accountable to over-alkylation products and starting material. Repeated attempts did not improve on this result by any significant degree, and the use of sodium hydride as base afforded an inferior yield of **116**. Purification also proved to be troublesome, as the various methylated products possessed very similar R_f values by

TLC. In addition, **116** is rather volatile which led to substantial losses of product when concentrating the chromatography fractions *in vacuo*.

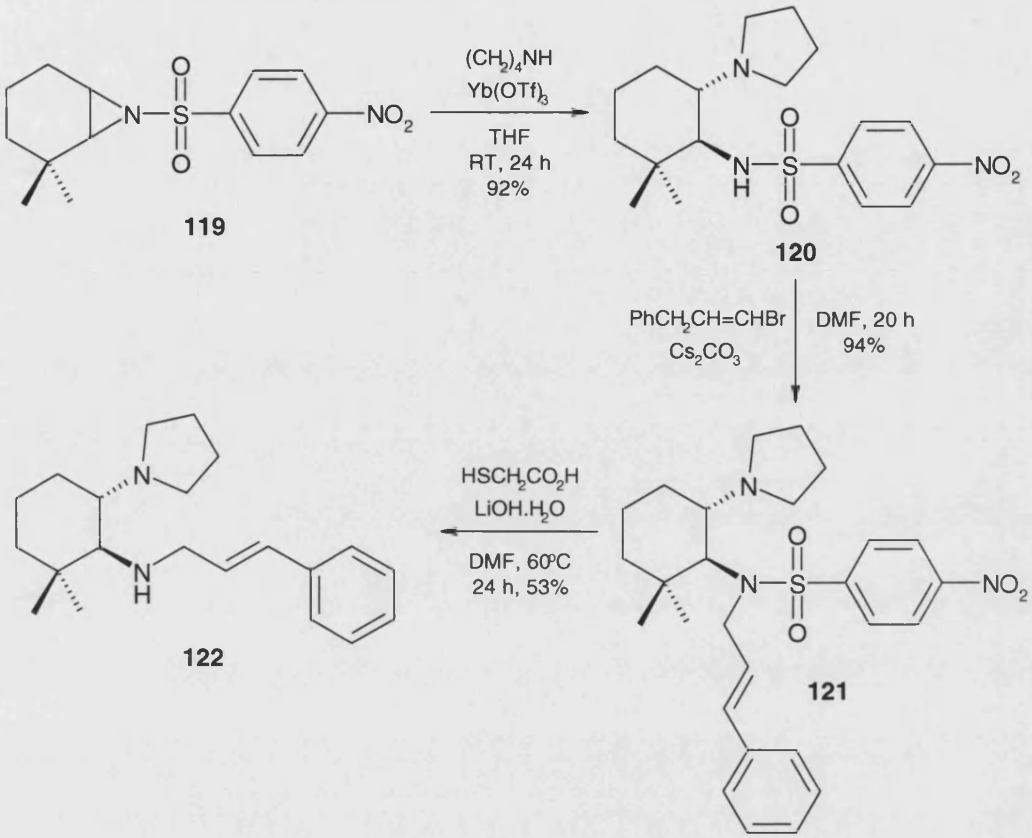
The conversion of **116** to alkene **118** has previously been reported in the literature[170] in a two-step methodology utilising the Shapiro reaction.[171] In this method, the ketone-derived hydrazone is converted to a dianion using an alkyllithium base which is decomposed directly to the vinyl anion; aqueous quenching then affords the corresponding alkene. It was envisaged that a more convenient separation of the various products of the alkylation step could be achieved by converting the crude **116** directly to the crystalline tosylhydrazone. Hence the residue obtained from methylation of **115** was heated with 1 equivalent of toluenesulfonylhydrazide in ethanol for 3 hours. TLC of the reaction mixture indicated that a greater difference in polarity (~0.2 between the mono- and di-methylated compounds) now existed between the various products of alkylation, greatly facilitating their separation by column chromatography; however, further experimentation found that the desired **117** could be made to crystallise directly from the crude oil by storing at low temperature (-10 to -20°C) for several days. Separation of the crystals by facile suction filtration and washing with ethanol afforded satisfactory 40-50% yields of **117** after thorough drying.

Decomposition of hydrazone **117** to the corresponding alkene **118** was achieved by the Shapiro reaction as stated above. The procedure of Hassner *et al.*[170] relating specifically to the preparation of **118** was employed, although it was decided to conduct the addition of methyllithium at -78°C rather than 0°C as recommended by Törmäkangas[172] and co-workers in their detailed investigation of the Shapiro reaction. Upon removal of the cooling bath, it was observed that formation of the dianion (indicated by a deep red colour) and subsequent decomposition (indicated by the vigorous evolution of nitrogen) occurred at temperatures far below 0°C - it was therefore somewhat surprising that addition of the alkyllithium reagent at this temperature was stipulated by the original authors.[170] A modified work-up procedure was devised which eliminated the need for distillation and afforded **118** in a high state of purity by NMR: after extraction of the crude product into pentane, the combined organic layers were concentrated *in vacuo* to ensure complete removal of the diethyl ether; further pentane was then added, which dissolved hydrocarbon **118** but left residual hydrazone **117** as insoluble white particles; suction filtration through

Celite® followed by rinsing of the filter pad with pentane afforded a clear filtrate which was cautiously concentrated *in vacuo* (using relatively high pressure to avoid co-evaporation of **118**) to leave alkene **118** which was used directly in the next stage without further purification.

Now that a viable route to **118** had been established, it remained to convert the alkene to its corresponding nosyl-aziridine to give the target model compound **119**. The successful aziridination of cyclohexene with nitrene precursor **110** and $Cu(OTf)_2$ gave support to the preparation of dimethyl-analogue **119** using this protocol. Thus **118** was reacted with freshly prepared **110** to afford a 57% yield of **119** after purification. It is possible that the lower yield of aziridine obtained from **118** may be caused by the *gem*-dimethyl group impeding approach of the metal-nitrene complex to the double bond, thus resulting in a slower reaction and competing decomposition of **110** (Taylor *et al.*[130] report that the addition of $Cu(OTf)_2$ to a suspension of nitrene precursor **110** causes it to decompose rapidly in the absence of an alkene substrate).

Model compound **119** was converted to the corresponding pyrrolidine *trans* diamine using an identical synthetic strategy to that outlined for **114** (Scheme 43). Reaction of **119** with pyrrolidine and $Yb(OTf)_3$ afforded an excellent yield (92%) of the ring-cleavage product **120**, with complete regioselectivity being observed. It was discussed above that the primary rationale for synthesising a dimethyl analogue of model compound **111** was to investigate possible steric hindrance of this group on alkylation of the secondary sulfonamide moiety. In the case of **120**, it was thought that deprotonation of the sulfonamide might be somewhat retarded by the presence of the dimethyl group. This would subsequently increase the lifetime of unreacted halide in the reaction mixture, which in turn may lead to decomposition in the case of light or temperature-sensitive halides (*e.g.* cinnamyl bromide), or competing substitution reactions involving nucleophilic attack of the base on the halide. In an effort to minimise such occurrences, potassium carbonate was replaced with the more powerful base cesium carbonate. Thus, **120** was reacted with 2 equivalents of Cs_2CO_3 and 1.5 equivalents of cinnamyl bromide; purification afforded a very high (94%) yield of tertiary sulfonamide **121**, indicating that the alkylation process was not significantly attenuated by the geminal dimethyl group.



Scheme 43 (Synthesis of model compound **119** and subsequent conversion to diamine **122**)

Deprotection of **121** was this time attempted using the second of the two methods given by Fukuyama *et al.*[162] employing LiOH and $HSCH_2CO_2H$. This method possesses an advantage over the $PhSH/K_2CO_3$ system in that the carboxylic acid group of mercaptoacetic acid allows the by-product of nosyl cleavage to be removed by simple base extraction of the crude reaction mixture. Treatment of **121** using this protocol resulted in a rather slower reaction than had been observed during deprotection of **113**; TLC analysis indicated an approximately 70% consumption of **121** after 24 hours at room temperature. Increasing the temperature to 50°C did not appear to greatly accelerate the reaction; completion was eventually achieved by addition of a further 2 equivalents of $HSCH_2CO_2H$ and 3 equivalents of LiOH with heating at 60°C for 16 hours. Basic extraction of the by-product as discussed above was performed, although column chromatography was still required to remove other minor side-products. A satisfactory (53%) yield of diamine **122** was subsequently obtained using this deprotection procedure, though rather inferior to that afforded

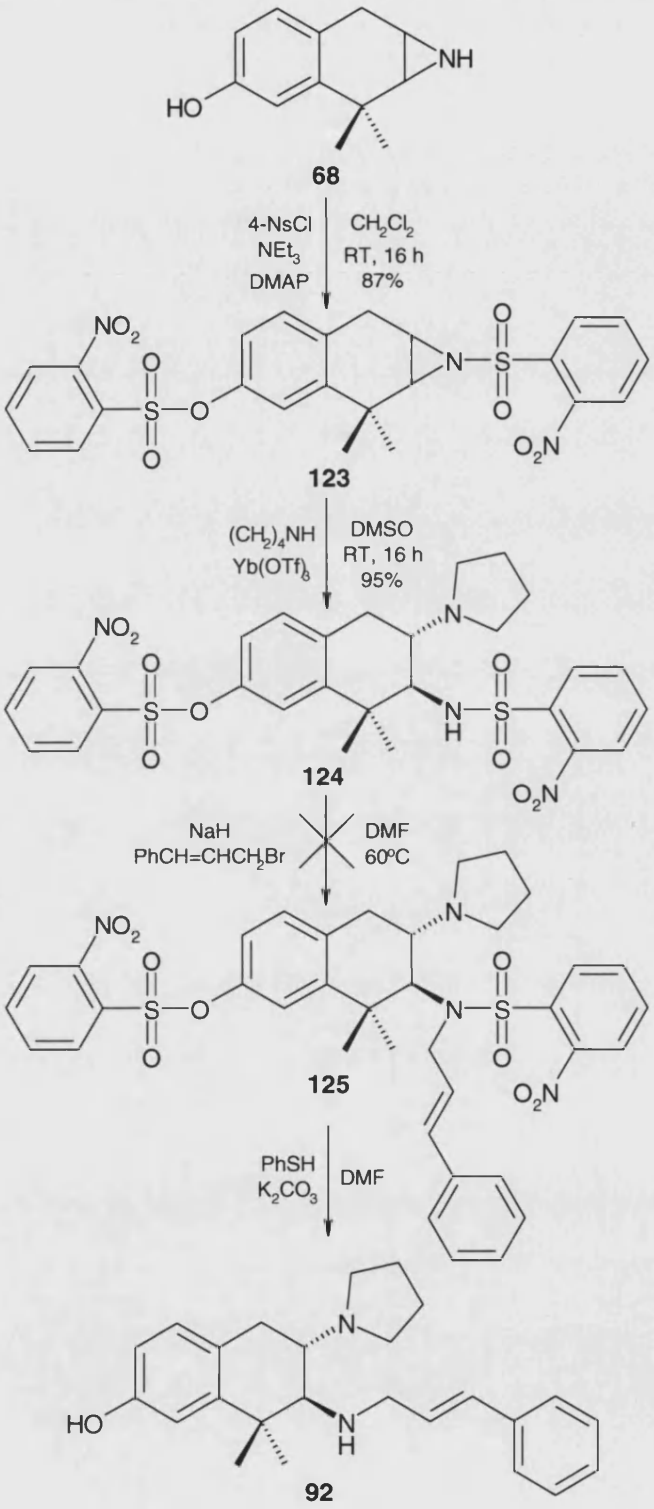
using the previous $PhSH/K_2CO_3$ method of cleavage; however, chromatographic purification of **122** was found to be more facile as the majority of thiol-containing by-products were removed during the work-up stage.

4.4.3 Synthesis of aminotetralin-based diamines bearing tertiary 3-substituents

The successful application of the nosyl protecting group to the synthesis of structurally-simplified *trans*-diamines **114** and **122** gave strong support to the application of this strategy to the synthesis of the desired aminotetralin diamines **92-94** (p. 82). Whilst the model nosyl-protected aziridines **101** (p. 90) and **119** (p. 101) were prepared directly from alkenes by copper-catalysed nitrene transfer, it appeared that synthesis of the corresponding aminotetralin nosyl aziridine would be most easily achieved by sulfonation of *N*-unsubstituted aziridines **67** or **68** (Scheme 22). It was initially envisaged that an analogous synthetic strategy to the attempted Boc and Cbz activation routes described in Section 4.3.1 would provide a convenient pathway to the 3-pyrrolidine ligand **92** (Scheme 44) - such a route is not appropriate for the preparation of **93** or **94** as the secondary amine group would undergo alkylation concurrently with the sulfonamide moiety.

Sulfonation of the aziridine and phenolic moieties of **68** with 2-nitrobenzenesulfonyl chloride (somewhat less expensive than 4-NsCl and reported by Fukuyama *et al.*[162] to be equally effective) proceeded relatively cleanly to afford a high yield of **123** as a solid. The acquisition of satisfactory NMR spectra of **123** was severely hampered by its lack of solubility in organic solvents - CH_2Cl_2, $CHCl_3$, THF, MeOH, DMF and DMSO all proving unsuccessful. It is highly likely that this is a result of strong intermolecular forces arising from the presence of numerous polar bonds in the structure of **123**.

Ring-opening of **123** with pyrrolidine in the presence of $Yb(OTf)_3$ was initially attempted in THF according to the previously described protocol; however, it was found that little consumption of **123** occurred even after prolonged reflux. Repetition of the reaction in CH_2Cl_2 afforded a similar result, most likely explained by the lack of solubility of **123** in these solvents. With continued experimentation, it was eventually found that **123** was soluble in a large excess of the highly polar aprotic solvent DMSO (dipole moment = 3.96), and a high yield (95%) of the ring-cleavage product **124** was obtained after stirring for 16 hours at room temperature.

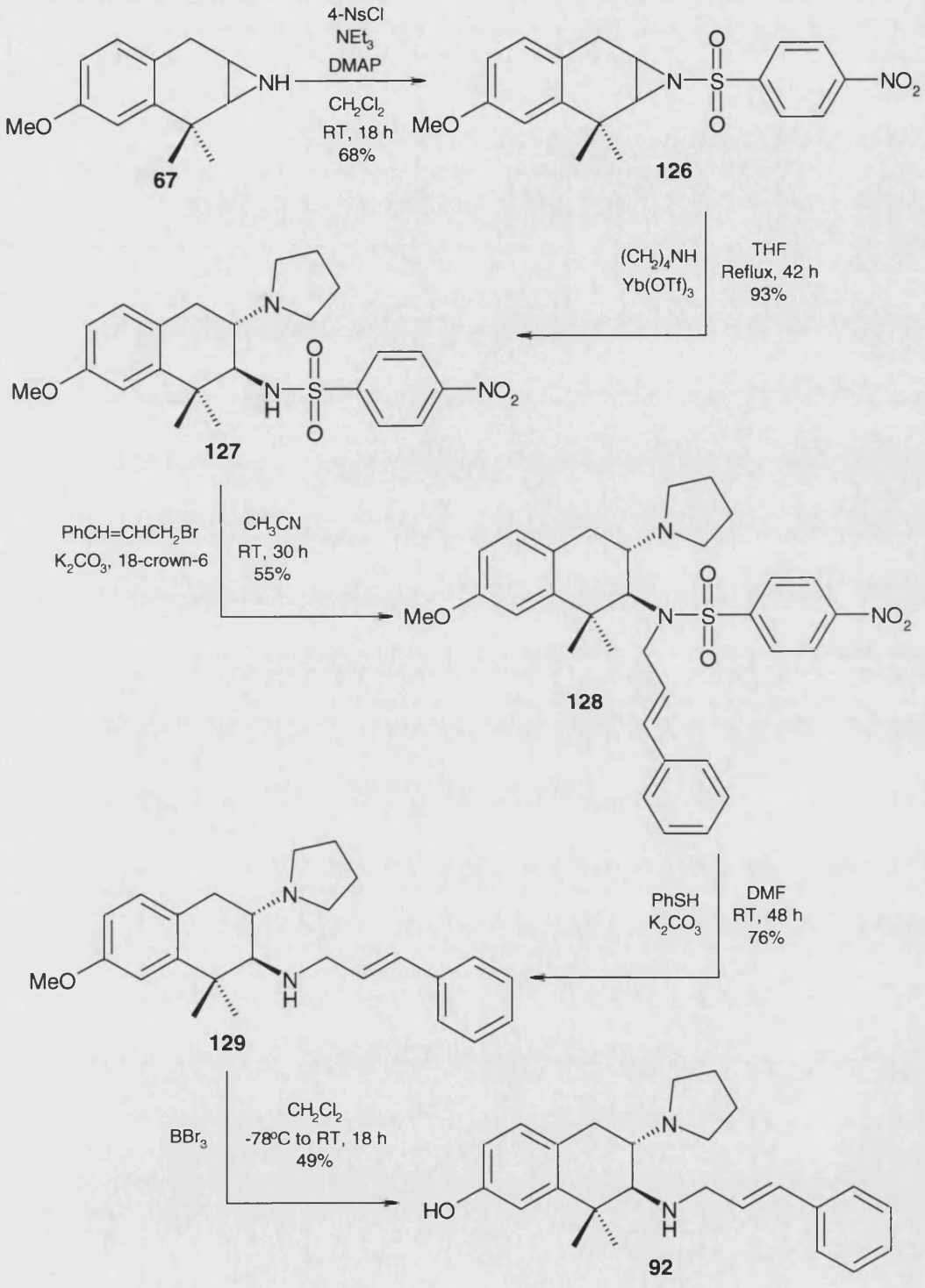


Scheme 44 (Synthetic route initially envisaged for ligand **92**)

Although alkylation of the sulfonamide group of **120** with cinnamyl bromide proceeded with high efficacy, analogous alkylation of **124** proved rather less straightforward. Indeed, no evidence of alkylation was apparent at room temperature even when utilising the powerful base sodium hydride; heating the reaction system to 60°C appeared to result in degradation of the components. The reason for this lack of reactivity is not clear, but owing to the additional difficulties encountered due to lack of solubility of di-nosylated aziridine **123**, it was decided that this synthetic pathway would not provide a convenient general route for the preparation of the desired ligands. Investigation of an alternative pathway was therefore undertaken.

In order to overcome the aforementioned solubility problems, it was decided to restrict the role of the nosyl group to purely that of an aziridine activating substituent and to utilise a different protecting group for the phenolic moiety. Aminotetralin aziridine **67** (p. 60) appeared an ideal starting point for such an investigation, as the methyl ether protecting group would enhance solubility of the synthetic intermediates in organic solvents rather than inhibit it as appeared to be the case for the nosyl group. Scheme 45 illustrates the proposed synthetic pathway.

Nosylation of aziridine **67** was achieved using 4-NsCl to afford *N*-substituted **126** in 68% yield after purification. It was decided to revert to the 4-nitrobenzenesulfonyl activating group as used in the successful synthesis of model diamines **114** and **122** in order to exclude any 'hidden' attenuating effects that the 2-nitrobenzenesulfonyl group may have exerted on reactivity of the sulfonamide moiety in compound **124**. Treatment of **126** with pyrrolidine and $Yb(OTf)_3$ at room temperature was expected to readily afford masked diamine **127** as had consistently been observed with the previous nosyl-protected aziridines investigated. TLC analysis of the reaction mixture, however, revealed that only slight consumption of **126** had occurred after 18 hours. Heating the system at reflux appeared to accelerate the reaction, although 42 hours were required to achieve total conversion to **127**. The initial attempt to alkylate secondary sulfonamide **127** with cinnamyl bromide was made using cesium carbonate in DMF. Encouragingly, a 53% yield of the desired **128** was obtained after 18 hours at room temperature, a striking improvement to the lack of reactivity observed when attempting to alkylate di-nosylated **124**. In an effort to improve the convenience of the reaction work-up, it was decided to evaluate the use of potassium carbonate with catalytic 18-crown-6 in acetonitrile as an alternative alkylation system.



Scheme 45 (Alternative synthetic route used to prepare ligand **92**)

The K_2CO_3/18-crown-6 method was originally reported by Åhman *et al.*[159] in conjunction with the *N*-alkylation of aziridines (see Section 4.3.2). It was envisaged that the crown ether would increase the solubility of the carbonate anion in acetonitrile, eliminating the need for DMF which is markedly more time-consuming to evaporate. Reaction of **127** under these conditions was found to result in a slower reaction, although an approximately 55% yield of **128** was obtained after stirring for 30 hours. The facile work-up of this latter method made it somewhat more attractive than the original method of Fukuyama *et al.*[162] and would be of particular value when performing such a reaction on a multigram scale.

Cleavage of the nosyl group from the model compounds was found to occur more readily using the reagent system $PhSH/K_2CO_3$ rather than $HSCH_2CO_2H$/LiOH and it was therefore decided to attempt deprotection of **128** using the former method. The reaction proceeded without complication and was complete after 48 hours at room temperature. Analysis by TLC revealed a certain amount of streaking of the product diamine, suggesting that slight decomposition was occurring on the silica gel. As it appeared unlikely that **129** could be readily purified by other means, it was decided to subject the residue to column chromatography using 1% triethylamine in CH_2Cl_2 as the eluant. The use of the stronger base triethylamine instead of ammonia was to ensure that the acidicity of the silica gel was sufficiently regulated to minimise decomposition of the diamine during purification. This technique was found to be successful, and a pleasing 94% yield of **129** was obtained.

From analysis of the ^{1}H NMR spectra of intermediates **127-129** (Figure 17), it was apparent that the presence of the nosyl group at the 2-position in **127** and **128** was influencing the chemical shift of the two methylene groups adjacent to the pyrrolidine nitrogen. In secondary sulfonamide **127**, the aforementioned groups appear as two multiplets, each integrating to two protons and separated by 0.10 ppm. Upon alkylation of the sulfonamide moiety with cinnamyl bromide, the separation between the two multiplets increases in **128** to 0.26 ppm. It would appear from these observations that steric crowding in the region of the vicinal diamine moiety somewhat impedes the rotation of the pyrrolidine group about the nitrogen/tetralin ring bond resulting in two distinct chemical environments for the methylene protons. The high degree of hindrance arising from the nosyl and cinnamyl group in **128** attenuates rotation to a greater extent than **127**, leading to an increase in separation of the two peaks in the ^{1}H NMR spectrum.

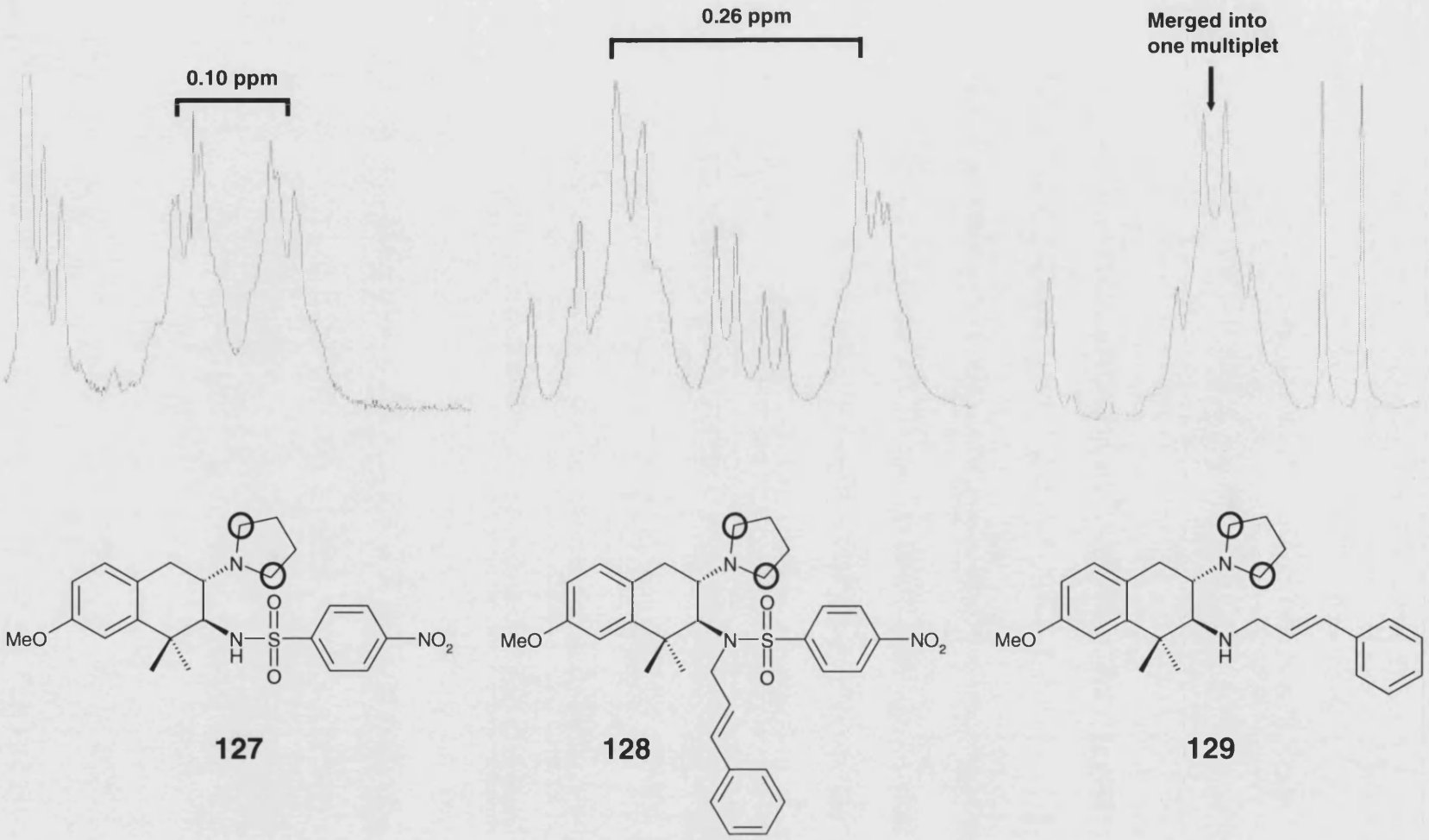


Figure 17 (Partial ^{1}H NMR spectra of **127-129** showing the effect of the nosyl group on the chemical equivalence of the pyrrolidine protons [shown circled])

It is interesting to note that coalescence of the peaks in **128** did not occur even when the spectrum was acquired at 50°C, indicative of the high barrier to rotation. Cleavage of the nosyl protecting group to afford **129** releases the pyrrolidine group from its rotational restriction, causing the methylene protons to merge into the typical 4-proton multiplet characteristic of this heterocycle.

The final step in the synthesis of ligand **92** (Scheme 45) was cleavage of the aromatic methyl ether. A major concern was that acidic *O*-demethylation methods might lead to similar difficulties in the partitioning of the crude product as was observed for **96**. With this in mind, it was decided to initially employ sodium 1-propanethiolate (prepared from sodium hydride and 1-propanethiol in DMF) to effect this reaction, being neither a significantly acidic nor basic reagent. Heating methyl ether **129** with 9 equivalents of NaSPr at 120°C for 24 hours, however, resulted only in a trace of product being apparent by TLC. A far more successful result was obtained by treating **129** with 3 equivalents of boron tribromide and quenching using the triethylamine/MeOH protocol designed for the acid sensitive aziridine **68**. By this method, a 49% yield of the desired ligand **92** was successfully obtained after purification.

To summarise, the chemistry developed with the aid of model compounds utilising the nitrobenzenesulfonyl group was found to be a convenient pathway for the synthesis of aminotetralin *trans*-diamine ligands where the 3-substituent is a tertiary nitrogen (as in **92**). It now remained to ascertain whether this chemistry could be extended to the preparation of diamine ligands bearing secondary amine groups at the 3-position.

4.4.4 Synthesis of aminotetralin-based diamines bearing secondary 3-substituents

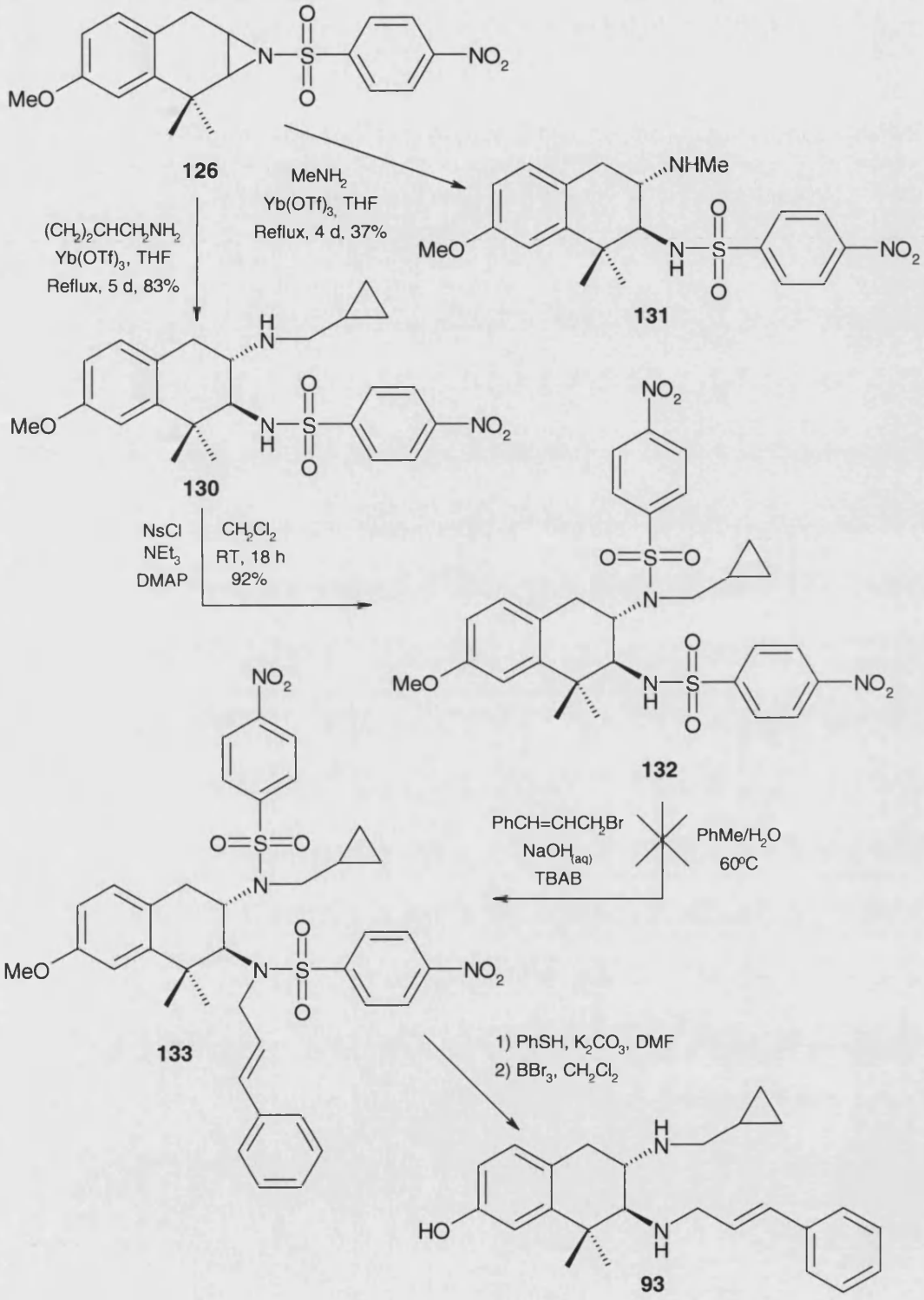
In a previous discussion, it was established that the original synthetic route involving a tertiary pyrrolidine 3-substituent would not directly transfer to the preparation of vicinal diamines bearing secondary 3-substituents such as **93** and **94** (p. 82) as alkylation of the sulfonamide moiety would lead to concurrent alkylation of the amine group. The development of a modified synthetic pathway incorporating an additional protection step for the secondary amine group appeared the most logical solution to this problem.

The penultimate step in the synthesis of ligand **92** (Scheme 45) is cleavage of the nosyl protecting group to afford the free diamine. As this reaction has been shown to proceed with high facility, it appeared that the nosyl group would also be most suitable for protection of the secondary amine functionality at the 3-position which results from attack of the primary amine nucleophile on the aziridine ring - removal of both protecting groups could then be effected in one step. The pathway envisaged for secondary 3-substituted diamines is depicted in Scheme 46.

Ring-opening of aziridine **126** with *N*-cyclopropylmethylamine (*N*-CPM) proceeded at an equally slow rate to the corresponding reaction with pyrrolidine, requiring a total of 5 days at reflux to achieve an 83% yield of **130**. To investigate whether a different catalyst might increase the rate of conversion, the reaction was repeated using 10 mol% $B(C_6F_5)_3$ in acetonitrile (see Section 4.3.2). Monitoring of the reaction by TLC indicated that the rate of consumption with $B(C_6F_5)_3$ was equally slow as with $Yb(OTf)_3$; a 74% yield of **130** was obtained after 3.5 days at reflux.

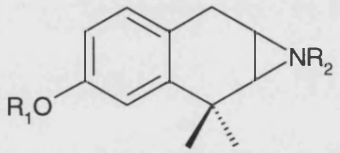
Ring-cleavage of **126** was also attempted using methylamine (solution in THF) as the nucleophile, although loss of the amine resulted in an even slower rate of reaction than *N*-CPM. In an effort to compensate for this, additional portions of methylamine solution were added periodically although only a 37% yield of the ring-opened product **131** was obtained after 4 days at reflux. It is likely that a superior yield could be obtained by the use of a sealed-tube system to prevent loss of methylamine. Due to time restrictions, however, it was decided to develop the synthetic route using the *N*-CPM product **130** which was more rapidly accessible.

It is interesting to consider at this stage the conditions required to effect ring-opening of the activated aziridines synthesised during this project. When the observations are compiled together (Table 13), a particular pattern is apparent. It appears that those aziridines possessing an electron-withdrawing phenolic group (Boc, Cbz, Ns) readily undergo ring-cleavage at room temperature, whereas **126** which possesses an electron-donating methyl ether group requires high temperatures and long reaction times to effect the same transformation. The lack of reactivity of **126** is very unusual for a nosyl aziridine as such activating groups are consistently reported as being extremely efficient promotors of aziridine ring-opening.[127,140,163] A possible explanation for these observations is apparent, however, if one considers the electron density of the carbon *p*-orbitals of the aromatic ring. In aziridine **126**, the methyl ether group donates electron density towards the aromatic ring via its oxygen



Scheme 46 (Initial synthetic pathway envisaged for secondary 3-substituted diamines)

lone pairs. It is proposed that this could promote intermolecular stacking of the aromatic groups (through interaction of carbon *p*-orbitals) making the aziridine carbon less accessible for nucleophilic attack. As electron-donating groups particularly enhance the electron density of those carbon atoms at the *ortho* and *para* positions, it may also be hypothesised that the *p*-orbital of the *para* aromatic carbon atom might attenuate the reaction by donating electron density towards the aziridine carbon at the 3-position thus decreasing its electropositivity and therefore susceptibility to attack. The electron-withdrawing groups of aziridines **69**, **97** and **123** decrease aromatic electron density and consequently have the reverse effects.



Aziridine	R_1	R_2	Nucleophile	Conditions required to cleave
69	Boc	Boc	Pyrrolidine	Room temperature for 18 h
97	Cbz	Cbz	Pyrrolidine	Room temperature for 18 h
123	Ns	Ns	Pyrrolidine	Room temperature for 16 h
126	Me	Ns	Pyrrolidine	Reflux for 42 h
126	Me	Ns	*N*-CPM	Reflux for 120 h
126	Me	Ns	Methylamine	Reflux for 96 h (incomplete)

Table 13 (Conditions required to effect aziridine ring-opening)

The next stage of the synthesis required protection of the exposed secondary amine moiety at the 3-position. Reaction of **130** using 4-nitrobenzenesulfonyl chloride proceeded in excellent (92%) yield, theoretically allowing the secondary sulfonamide group to react selectively with the desired halide. Attempted alkylation of **132** with cinnamyl bromide and cesium carbonate in DMF, however, proved unsuccessful: no reaction was evident by TLC after 16 hours at room temperature nor after a further 4 hours at 60°C. Examination of the 3D structures of **130** and **132** (Figure 18 – structures generated using the "3D Structure Optimization" facility on ChemSketch[114] and exported to RasMol[115]) reveals a significant change in

conformation of the cyclohexene ring when the *N*-CPM moiety is protected with 4-nitrobenzenesulfonyl chloride. This is indicative of the steric requirements of the two bulky nosyl groups in **132**, and directly leads to the suggestion that the subsequent introduction of a cinnamyl group may place too many steric demands on the system. Kas'yan *et al.*[173], however, report the successful alkylation of hindered norbornene sulfonamides under phase transfer conditions. Using this protocol, a solution of **132** and cinnamyl bromide in toluene was vigorously stirred with aq. 12.5M NaOH at 60°C for 15 hours. TLC of the organic layer indicated that a reaction had occurred, but not cleanly. Unfortunately, column chromatography of the residue after work-up afforded no material that could be convincingly assigned to the required product **133** by ^{1}H NMR. It thus appeared unlikely that **132** would undergo alkylation efficiently, and it was consequently decided to seek an alternative route to ligand **93**.

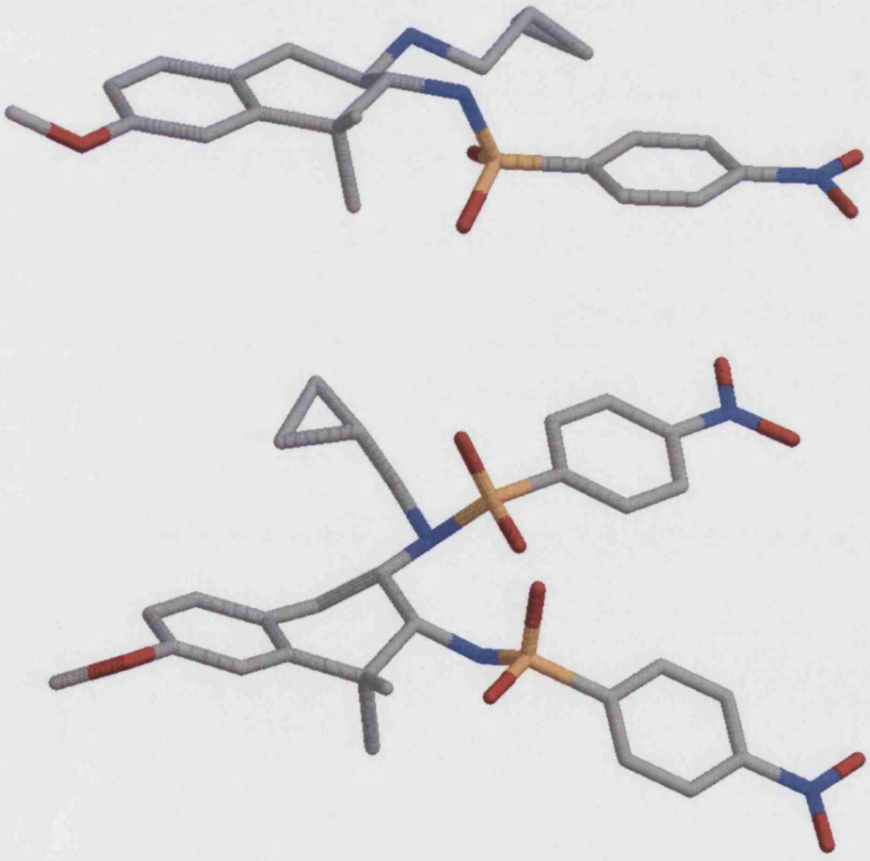
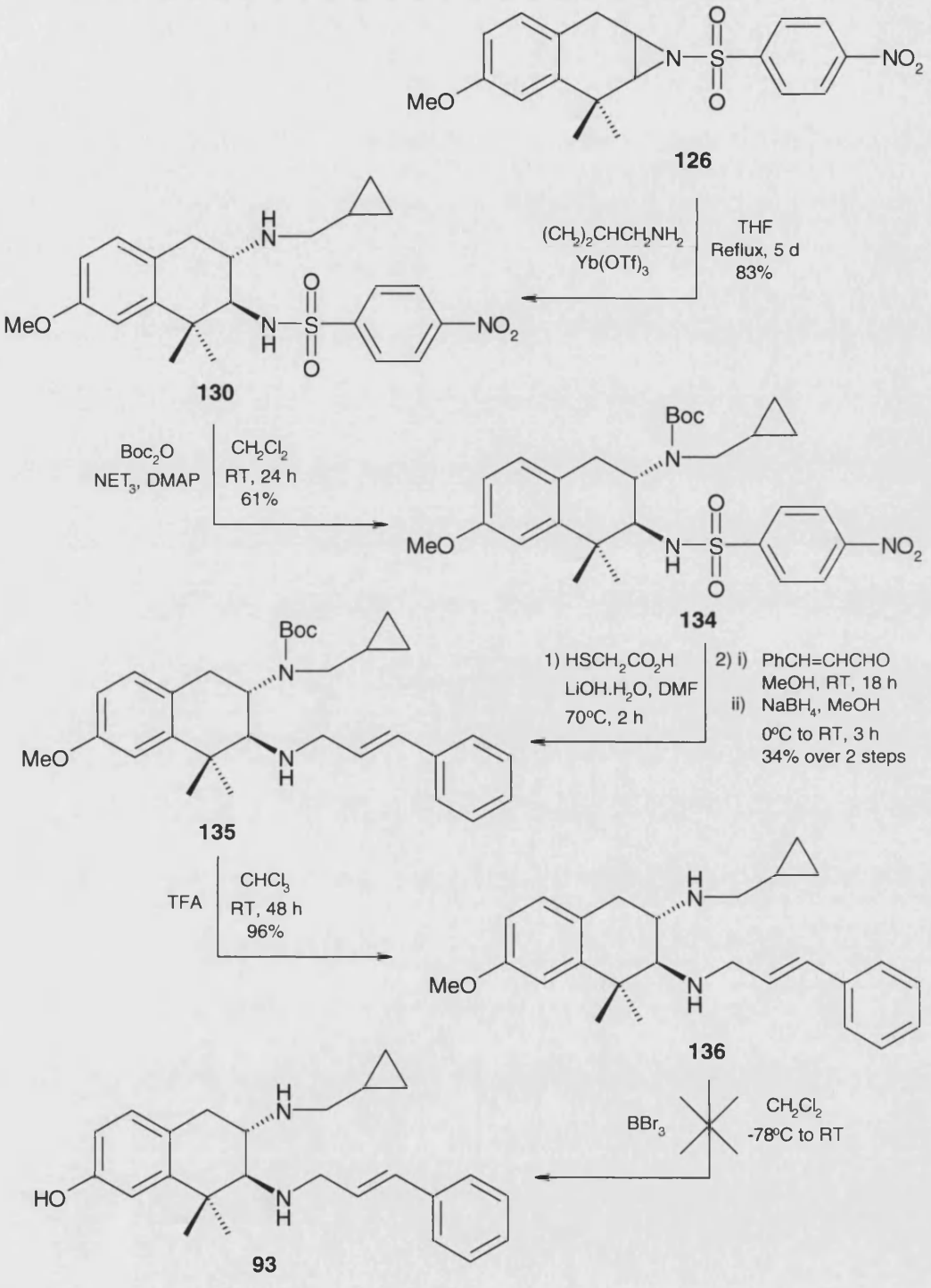


Figure 18 (Optimised structures of **130** (top) and **132** (bottom) illustrating the steric demands imparted by the second nosyl group)

It was thought that the aforementioned alkylation difficulties could be overcome by ensuring that introduction of the cinnamyl group was performed on a less sterically-hindered system than **132**. By analysis of Scheme 46, it appeared that one way to achieve this would be to cleave the secondary nosyl group at the 2-position immediately after protection of the *N*-CPM moiety. This would unmask the primary amine group which could be reductively alkylated with *trans*-cinnamaldehyde and sodium borohydride to introduce the desired side-chain. In order to accomplish this, an alternative protecting group unreactive towards thiolates would be required for the *N*-CPM moiety. With these concepts in mind, Scheme 47 was developed.

The Boc group was selected for protection of the *N*-CPM moiety due to its facile protection/deprotection methods and unreactivity towards most nucleophiles. Ring-opened compound **130** was therefore reacted with Boc_2O and catalytic DMAP to afford a moderate yield (61%) of protected **134** after purification. The presence of a closely-running product by TLC suggested that acylation of the secondary sulfonamide group may have been a competing reaction.

The reagents utilised for cleavage of the nosyl group were selected after much deliberation. Although $PhSH/K_2CO_3$-assisted deprotection had previously resulted in high yields of the unmasked amine, it was necessary to remove excess benzenethiol and the by-product derived from reaction of the thiolate anion with the nosyl group (*via* the Meisenheimer complex). This factor was relatively insignificant in the previous applications of this reaction, as the diamine product was considerably more polar than either of these two undesired substances and therefore separation was generally unproblematic. For the present case, however, the presence of a Boc group would decrease the polarity of the product which could result in purification difficulties if the R_f coincided with a by-product of the reaction. It therefore appeared prudent to use the alternative, $HSCH_2CO_2H/LiOH$ deprotection system where the by-product and excess reagent is removable by extraction with aqueous base. Reaction of **134** under these conditions afforded a rather low (48%) recovery of product after column chromatography, which unfortunately remained impure due to co-elution with a slightly more polar contaminant. Rather than attempting further purification at this stage with possible loss of valuable material, it was decided to proceed directly to the next step of the synthesis. An alternative deprotection system



Scheme 47 (Alternative synthetic pathway to secondary 3-substituted diamines)

which may afford better results has been reported by Farr and co-workers[174] who were prompted by disappointing results with the $HSCH_2CO_2H$/LiOH method to develop a novel nosyl-cleavage procedure using dodecanethiol and LiOH under phase-transfer conditions. This system is apparently highly effective and the lipophilicity of the dodecyl chain (far greater than PhSH) allows for facile removal of the by-products; in addition dodecanethiol is inexpensive and virtually odourless.

The primary amine resulting from denosylation of **134** underwent efficient reductive alkylation with *trans*-cinnamaldehyde using the two-step methodology discussed previously to smoothly afford a 71% yield of **135** (34% over the two steps). As expected, the contaminant from the previous step was now easily removed by column chromatography. Deprotection of the Boc group to yield **136** was achieved using TFA, although the process appeared to be somewhat slow and required 30 equivalents of acid to drive it to completion. ^{1}H NMR analysis indicated the reaction to be extremely clean, and no purification was required after basification of the residue and extraction according to the standard protocol.

The previously synthesised diamines **92, 114** and **122** were all found to be stable at room temperature for several weeks, but unfortunately this was not so for **136**. Due to unforeseen circumstances, it was necessary to delay cleavage of the methyl ether to afford **93** by one week after which time it was apparent by TLC that the compound had undergone substantial decomposition. This was unexpected given the stability of the other diamines and there was regrettably insufficient time to repeat the synthesis. In light of the instability of **136**, a revised protocol whereby *O*-demethylation is carried out immediately after cleavage of the Boc group would probably afford superior results; storage of **93** as its di-HCl salt under anhydrous conditions may assist in preventing similar degradation.

To summarise, this synthetic pathway shows considerable promise for the preparation of secondary 3-substituted diamines. Improvement of the nosyl deprotection procedure (perhaps by utilising the dodecanethiol method described) and subsequent measures to prevent decomposition of the unmasked diamines should result in a synthetic route enabling flexible variation of both the 2- and 3-substituents, thus giving access to a wide range of *trans*-diamine ligands.

4.4.5 Investigation of an alternative approach to vicinal diamines utilising an aziridinium ion intermediate

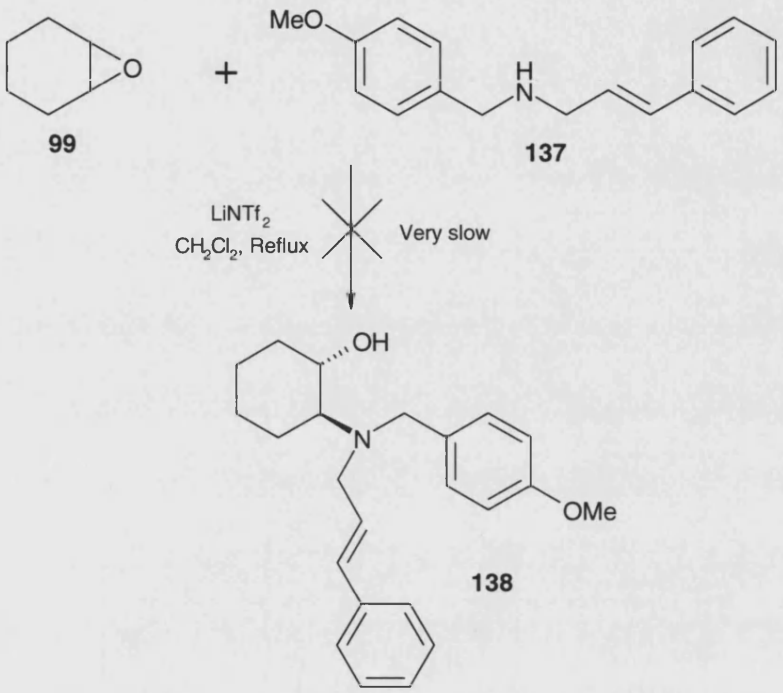
In Section 4.2, the possibility of using an aziridinium ion as a means of synthesising *trans*-diamines was discussed. The method involves reacting a *trans* amino alcohol (where the nitrogen must be tertiary) with methanesulfonyl chloride and mild base to transform the alcohol moiety to an efficient leaving group. Rapid intramolecular attack by the tertiary amine then occurs to afford an aziridinium ion, at which point a primary or secondary amine may be introduced which readily undergoes S_N2 attack with the ring to afford a *trans*-diamine.

A particular difficulty with applying such chemistry to the preparation of diamines **92-94** (p. 82) highlighted in Section 4.2 was the requirement of a tertiary amine centre. This appeared to limit the applicability of this approach to **92-94** as the amine at the 2-position is always required to be secondary. It appeared that a relatively simple way to overcome this problem would be to protect the secondary amine with a benzyl derivative, thus transforming the nitrogen to a tertiary centre whilst retaining its nucleophilicity. The 4-methoxybenzyl protecting group appeared ideal for this purpose, being more labile than the simple benzyl group and easily removed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[156]; this oxidative cleavage method also allows for the inclusion of unsaturation in the side-chain.

As the synthesis of a tertiary amino alcohol precursor based on the aminotetralin scaffold would require the planning of a new synthetic route, it was decided to again utilise a cyclohexyl-type model compound to evaluate whether such chemistry would provide a viable route to the required ligands. Scheme 48 depicts the initial one-step strategy envisaged for model compound **138**.

Secondary amine **137** was prepared in 49% yield from stepwise reductive alkylation of 4-methoxybenzylamine with *trans*-cinnamaldehyde and sodium borohydride. It was initially envisaged that **137** would undergo nucleophilic attack on cyclohexene oxide (**99**) in the presence of a suitable catalyst. The inexpensive weak Lewis acid lithium bistrifluoromethanesulfonimidate ($LiNTf_2$) has been reported as an efficient promoter of ring-opening reactions of epoxides with amines[175] and appeared a logical choice for the present investigation. Hence **99** was treated with 1.2 equivalents of **137** and 0.5 equivalents of $LiNTf_2$ in CH_2Cl_2 according to the literature protocol. However, only a trace of product was detectable by TLC after 24 hours at room temperature and heating the system at reflux for the

same length of time did not significantly drive the reaction forward. It therefore appeared that the bulkiness of **137** was severely attenuating its ability to effect ring-cleavage of **99** and an alternative approach to **138** would be required.



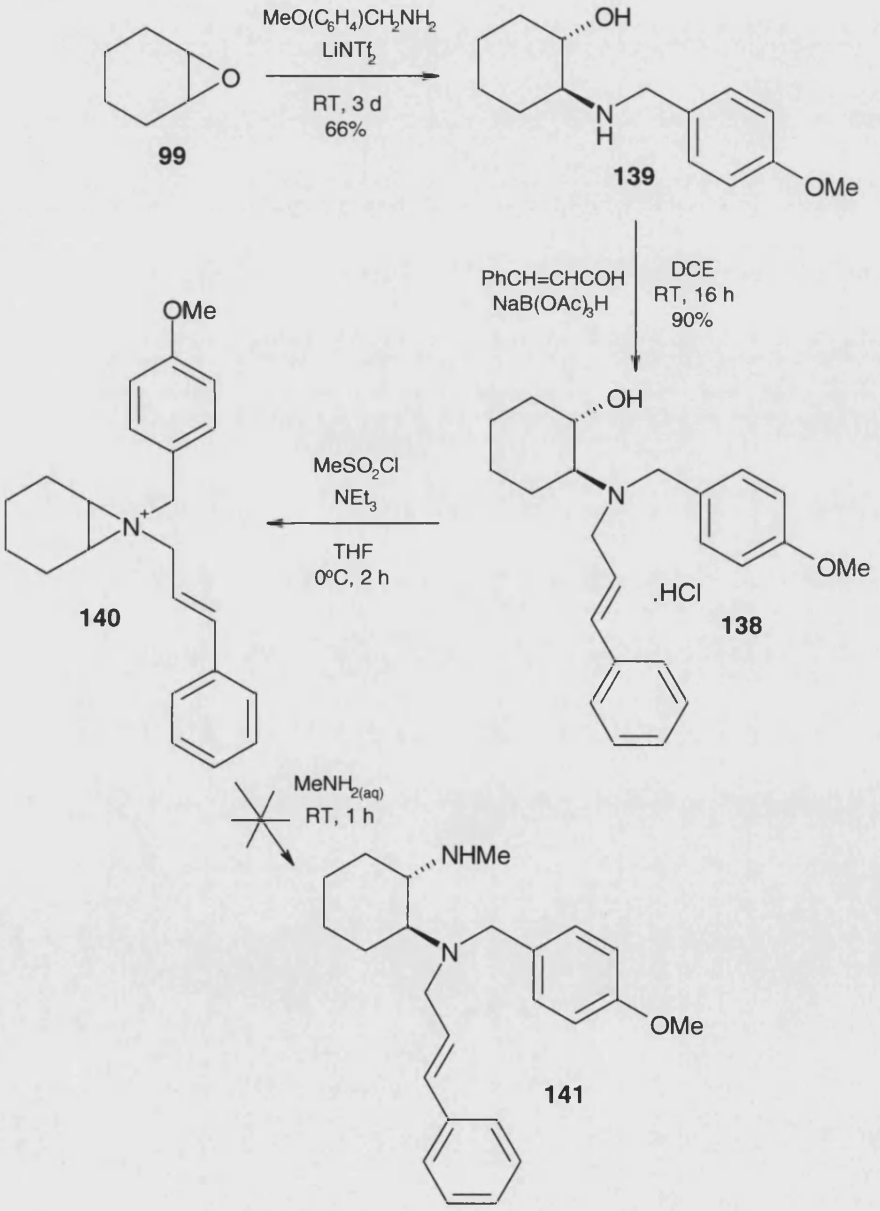
Scheme 48 (Initial synthetic route planned for model compound **138**)

It was invisaged that **138** could instead be constructed in a two-stage synthesis utilising 4-methoxybenzylamine rather than **137** as the ring-cleaving nucleophile (Scheme 49); such an approach would irradicate any difficulties arising from steric hindrance of the amine. Hence equimolar quantities of **99** and 4-methoxybenzylamine were stirred at room temperature with 0.2 equivalents of $LiNTf_2$ in the absence of solvent for 3 days. Conversion to the HCl salt and subsequent recrystallisation from propan-1-ol afforded a satisfactory (66%) yield of the *trans* secondary amino alcohol. Attempts to effect ring-cleavage in the presence of catalytic zirconium(IV) chloride[176] gave decidedly inferior results.

It appeared that the most facile way to introduce the required cinnamyl group selectively to the amine moiety would be by reductive alkylation. Indeed, treatment of **139** free base with *trans*-cinnamaldehyde and excess sodium

triacetoxyborohydride resulted in a very clean reaction; conversion to the HCl salt and recrystallisation gave tertiary **140**.HCl in excellent (90%) yield.

Previous literature examples of diamine preparation *via* aziridinium ion intermediates have always employed simple, 'symmetrical' *N*-substituents in the tertiary amino alcohol precursor *e.g.* dibenzyl (see Scheme 30), diethyl and piperidinyl.[146,153,154] Therefore, it was not known at this point whether more bulky, 'unsymmetrical' tertiary amines such as **138** would readily undergo ring-closure in an analogous manner.



Scheme 49 (Alternative synthetic route to **138** and attempted conversion to diamine **141**)

The protocol of de Sousa *et al.*[146] was utilised as it specifically focuses on the use of methylamine as the attacking nucleophile and was therefore of particular relevance to the present project. Accordingly, a suspension of **138**.HCl (as excess triethylamine was used in the procedure, it was decided that prior conversion to the free base was not necessary) in diethyl ether at 0°C was treated with 3 equivalents of triethylamine followed by 1.2 equivalents of methanesulfonyl chloride. After stirring for 30 minutes to allow the aziridinium ion to form, a large excess of aqueous methylamine solution was added. TLC of the crude reaction mixture after stirring overnight indicated the presence of mainly starting material, although a significant quantity of a less polar substance was evident as were traces of highly polar products near the baseline. Repetition of the reaction using the free base of **138** afforded similarly poor results. In the latter case it was observed that precipitation of triethylamine.HCl occurred upon addition of methanesulfonyl chloride to the system (consistent with the observations of de Sousa and co-workers[146]), suggesting that the spot of greater R_f in the crude TLC is the methanesulfonyl derivative of **138**.

A somewhat different result was obtained when the reaction was conducted at low temperature (below -20°C). TLC monitoring of the system indicated complete consumption of starting material 20 minutes after the addition of methanesulfonyl chloride. Two prominent spots on the plate were apparent: a product of lower polarity with R_f equal to that observed previously and a substance which remained on the baseline. This latter spot appeared to suggest the presence of the aziridinium intermediate **140**, although subsequent treatment with methylamine did not result in the formation of any prominent polar product by TLC. Interestingly, heating of the system instead of addition of methylamine was found to lead to conversion of the baseline product back to starting material **138**.

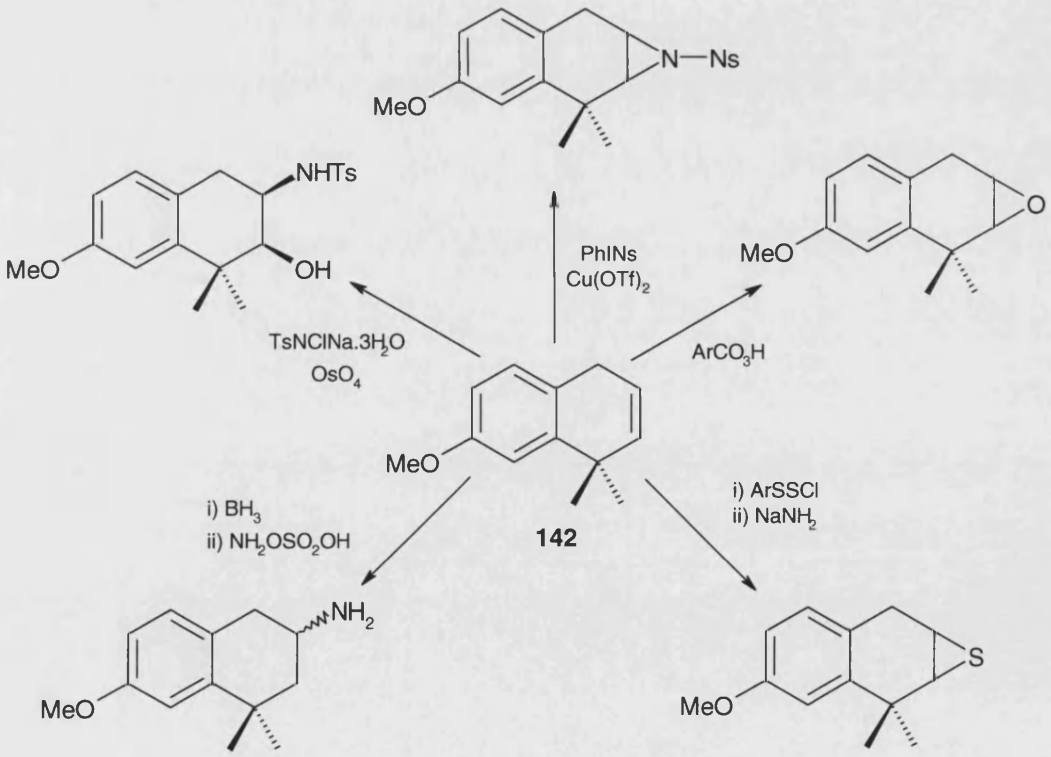
The above results appear rather ambiguous but suggest that formation of aziridinium ion **140** did occur to some extent, although its failure to then react with methylamine in the efficient manner reported for the literature examples suggests that the intermediate species was not stable. As the nosyl route of *trans*-diamine synthesis was proving to be considerably more successful, it was decided to discontinue investigation of the aziridinium method at this point and focus efforts elsewhere.

CHAPTER 5

INVESTIGATION OF A NEW COMMON INTERMEDIATE FOR LIGAND SYNTHESIS USING A CYCLISATION APPROACH

5.1 Design rationale

The alkene functional group is a highly versatile tool in organic synthesis, readily undergoing reaction with a vast range of electrophiles. Alkenes may thus be rapidly transformed to a variety of other functionalities including epoxides, aziridines and diols amongst others. It was thus envisaged that such an unsaturated moiety could be incorporated into the essential 1,1-dimethyltetralin structure to provide a new common intermediate, **142**, which would enable access to a far greater range of ligands than could be provided by oxime **37** (p. 31). Scheme 50 illustrates a few of the many possible functionalised structures which could be obtained from **142**.



Scheme 50 (Possible synthetic transformations of alkene **142**)

5.2 Synthetic studies

Perhaps the most obvious synthetic approach to alkene **142** is Shapiro reaction of the tosylhydrazone derived from 1,1-dimethyltetralone **36** (p. 31). In an analogous manner to 2,2-dimethylcyclohexanone (**116**) in Scheme 41, ketone **36** would be converted to its corresponding tosylhydrazone by heating with tosylhydrazide. This intermediate would then be expected to undergo decomposition in the presence of methyl or butyllithium to afford the desired alkene **141**. Such an approach has been previously applied successfully by Miller and co-workers[177] for the preparation of a similar 1,1-dibenzyltetralin compound.

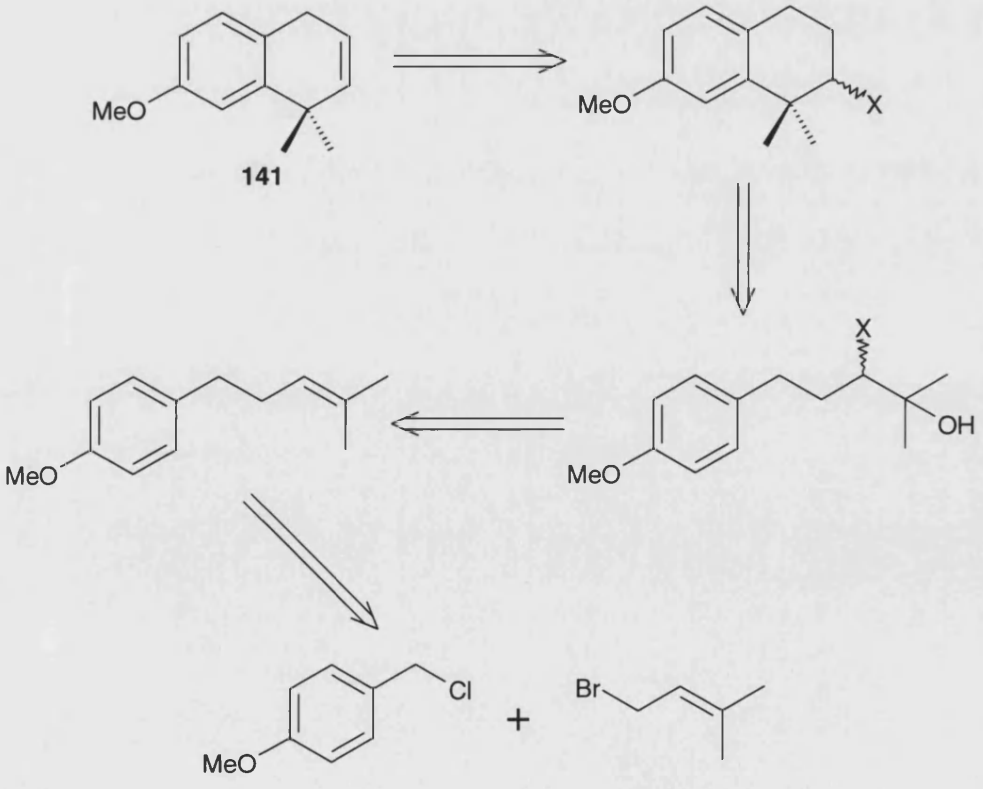
The many possible series of ligands which could be readily accessed from **141** require that the experimental procedures used to prepare alkene need to be robust, convenient and applicable enough to enable multigram quantities to be prepared. The synthesis of **141** *via* the Shapiro reaction as described above uses ketone **36** as its starting point, which in turn is prepared in three steps from 2,7-dihydroxynaphthalene (**46**). Consideration of the individual experimental procedures reveals several unsatisfactory aspects of this synthetic route:

1. The use of several highly hazardous reagents: dimethyl sulfate, iodomethane, metallic sodium and methyllithium.
2. Three out of the five steps require external heating and one must be conducted at low temperature (-78°C) – somewhat inconvenient for larger scale preparations (and refluxing solvents are a potential fire hazard).
3. The intermediate tetralone **35** is expensive when obtained commercially and its synthesis (though now improved) is rather time-consuming.

The above limitations of the initially envisaged synthetic route gave sufficient motivation for the investigation of alternative pathways. The presence of the 1,1-dimethyl group adjacent to the aromatic ring in **141** immediately suggests that formation of the cyclohexyl ring might be feasible *via* nucleophilic attack of the aromatic ring on a tertiary cation centre. The synthesis of tetralins by the acid-catalysed cyclodehydration of alcohols is a long established method for the preparation of such compounds[178] and is particularly successful when dehydration leads to a tertiary cation (as is the case where 1,1-disubstituted tetralins are the products) due to the stabilising effect of the alkyl groups. The convenience,

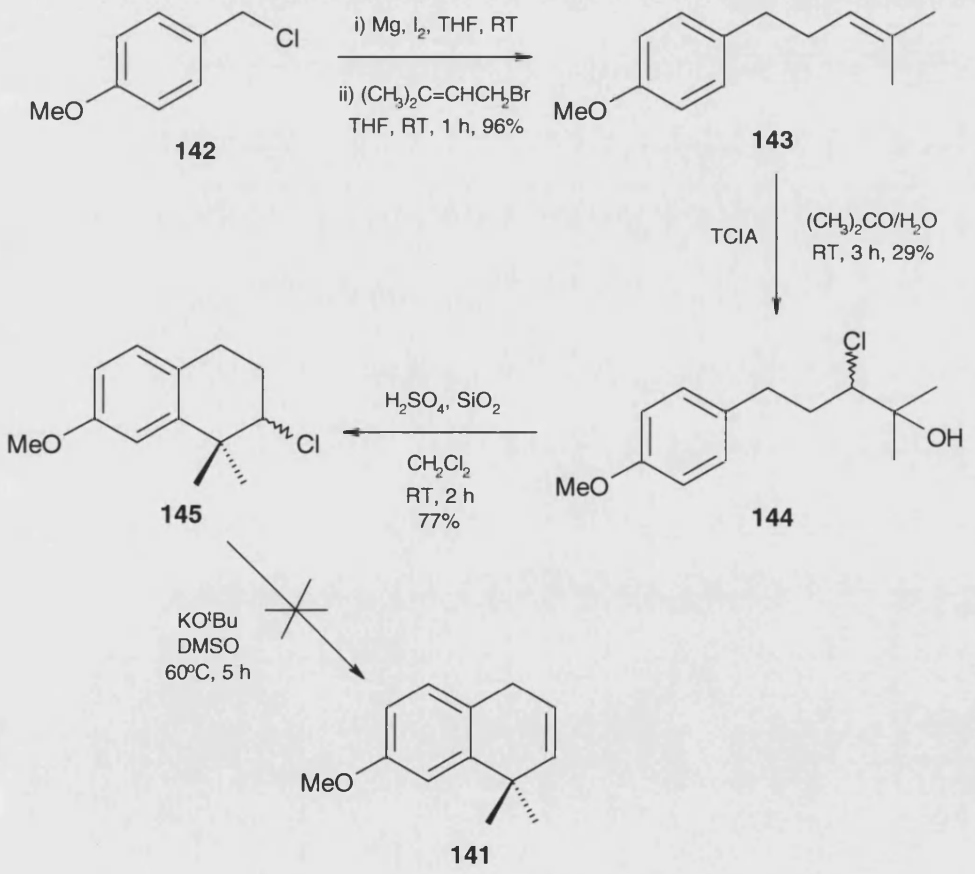
economy and low toxicity of such an approach made it seemingly ideal for the multigram scale of ligand precursor **141**.

One important factor which needed to be addressed was how the alkene moiety would be introduced in the required 2,3-position. The most straightforward, economical and reliable way to achieve this appeared to be the classical method of base-induced elimination. For this to occur, a suitably positioned leaving-group such as a Cl, Br, I, OMs, or OTs must be present in the molecule. In order to introduce the double bond in the 2,3-position required for **141**, the leaving-group must be vicinal to the tertiary alcohol moiety otherwise the conjugated 3,4-alkene would be the predominant elimination product. It is well know that halohydrins (1,2-haloalcohols) may be readily prepared from the corresponding alkene and it was therefore decided to use a halide as the leaving group in the elimination reaction. Retrosynthetic Grignard disconnection of the hydrocarbon chain of the parent alkene resulted in two commercially available and inexpensive halides as the starting materials of a four step synthesis of ligand precursor **141** (Scheme 51).



Scheme 51 (Retrosynthetic analysis of **141**)

Formation of the Grignard reagent from 4-methoxybenzyl chloride (**142**) was achieved by iodine-initiated reaction with pulverised magnesium turnings in anhydrous THF at room temperature. The formation of homodimers of **142** was evident in early attempts, but it was found that this could be entirely suppressed by efficient grinding of the magnesium turnings prior to reaction with the halide. Once a cooled solution of the Grignard reagent had been obtained, 1-bromo-3-methylbut-2-ene was cautiously added and the product subsequently isolated by standard aqueous work-up. If the reaction was performed carefully enough, it was found that purification was not required and the near quantitative yield of **143** obtained could be used directly in the next step.



Scheme 52 (Attempted synthesis of ligand precursor **141**)

Of the 4 stages of this synthetic pathway (Scheme 52), this initial step may be regarded as the most hazardous and least convenient due to the sensitive nature of the Grignard reagent; however, the fact that the reagent is prepared and immediately reacted with the bromide in the same flask greatly minimises any hazards resulting from the flammable/corrosive nature of the material. This should be compared directly with the Shapiro reaction which requires the user to transfer large quantities of methyllithium solution *via* syringe or cannula – undoubtedly a far more hazardous and inconvenient procedure.

Conversion of **143** to the halohydrin was initially attempted using the 'classical' method of *N*-bromosuccinimide in THF/water. This method generates hyperbromous acid (HOBr) *in situ* which may then undergo reaction with alkenes to afford bromohydrins.[97] In the case of **143**, reaction did not occur at all smoothly and many products were visible by TLC. This was not entirely suprising, as aromatic rings bearing activating substituents are highly susceptible to halogenation by a wide range of reagents including *N*-bromosuccinimide. A more selective method was therefore required.

Analysis of the literature revealed that the majority of systems used to transform alkenes to halohydrins were also reported to halogenate activated aromatic rings. Further investigation brought to attention the studies of Mendonça *et al.*[179] into the use of trichloroisocyanuric acid (TCIA) as an efficient reagent for the preparation of chlorohydrins. Although chloride ion is a less effective leaving-group than bromide, this method appeared very attractive as the reagent is extremely inexpensive and non-toxic; only 0.34 equivalents of the reagent are required (due to the presence of 3 chlorine atoms in the molecule); it is not reported to halogenate aromatic rings; and the reaction proceeds under mild conditions. Hence **143** was treated with 0.34 equivalents of trichloroisocyanuric acid in acetone/water at room temperature according to the literature protocol. TLC of the reaction mixture after 20 hours indicated a major product of higher polarity than **143** accompanied by a trace of a side-product of similar R_f. These were assigned as the desired **144** (Markovnikov addition) and other regioisomer (anti-Markovnikov addition) respectively. A small amount of starting material was also apparent (perplexingly, complete consumption of **143** could never be achieved even with excess reagent or prolonged reaction times) but the absence of other reaction products indicated that chlorination of the aromatic ring had not occurred. Column chromatography of the

crude product proved rather troublesome and resulted in partial decomposition of **144** (although the decomposition product was later identified as cyclised **145**). Attempted cyclisation of unpurified chlorohydrin, however, afforded very poor results indeed and it was therefore decided to conduct rough chromatographic purification in the presence of 1% triethylamine to inhibit tertiary cation formation. Removal of the unwanted regioisomer was not deemed to be necessary at this point as only the tertiary alcohol **144** was expected to undergo acid-catalysed cyclisation - it was thought that separation would be more facile after the next step of the synthesis and no further purification of the crude mixture was attempted.

Cyclodehydration reactions are most commonly carried out by treating a solution of the alcohol with a neat acid, typically sulfuric or polyphosphoric acid.[178]; heating is often required to obtain good yields of the tetralin. Kropp and co-workers[180], however, report that greater yields of tetralins may be obtained by utilising acid pre-absorbed onto the surface of activated silica gel. In this method, a suspension of silica gel in CH_2Cl_2 is treated with neat acid (phosphoric acid is reported as being particularly efficient for this purpose) and the mixture stirred to allow absorption to occur. A solution of the alcohol is then introduced and stirring continued at room temperature until cyclodehydration is complete (completion of the reaction generally occurs within 2 hours). This protocol appeared highly convenient, economical and reasonably environmentally friendly, fulfilling the requirements of the current project.

Treatment of crude chlorohydrin **144** with 1 equivalent of phosphoric acid according to the conditions of Kropp *et al.*[180] failed to effect cyclisation to the desired **145**. Further experimentation, however, revealed that cyclodehydration was extremely efficient when a solution of **144** in CH_2Cl_2 was slowly added to 2 equivalents of neat sulfuric acid absorbed onto silica gel. The reaction was consistently complete within 2 hours and required only facile column chromatography to afford a high (77%) yield of 2-chloro-1,1-dimethyltetralin **145**. As expected, the corresponding regioisomer of **144** remained unchanged after exposure to acid and was very easily removed during purification.

A vast number of reagents are reported in the literature for the elimination of alkyl halides, particularly common systems being alcoholic potassium hydroxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and potassium *tert*-butoxide in DMSO. Since there was no literature precedent for the dehydrochlorination of a tetralin-like

compound, it was decided to initially utilise KO^{t}Bu in DMSO as this system was successfully applied to the dehydrochlorination of chlorocyclodecane.[181] Whereas the authors report that room temperature is sufficient to effect elimination, treatment of **145** under these conditions resulted in no reaction. Heating the system to 40°C similarly afforded no reaction, although at 60°C elimination was found to occur. Analysis of the ^{1}H NMR spectrum after aqueous work-up confirmed that dehydrochlorination had indeed occurred, but it was apparent that the desired 2,3-alkene **141** had rearranged to the thermodynamically-favourable conjugated form **146** (Figure 19).

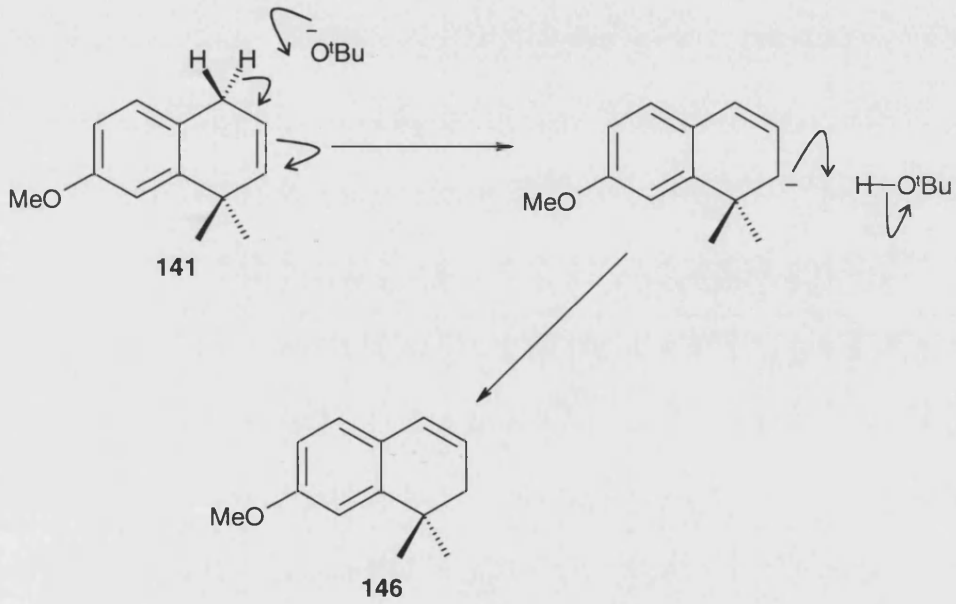
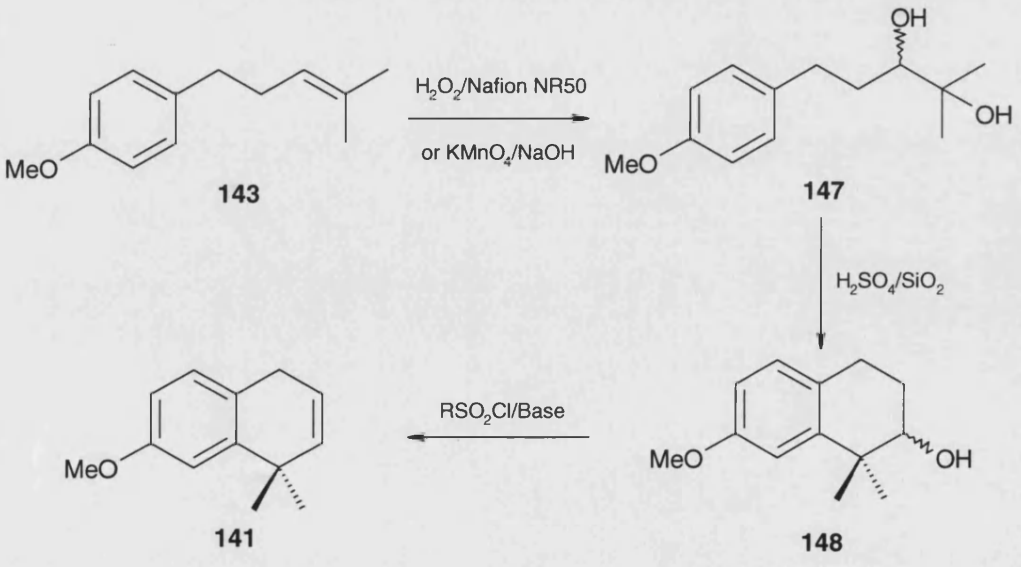


Figure 19 (Rearrangement of alkene **141** in the presence of potassium *tert*-butoxide)

This type of rearrangement has been reported previously by Miller *et al.*[177] for a similar 2,3-unsaturated tetralin system at elevated temperatures. It was expected that dehydrochlorination of **145** would proceed without the need for heating thus avoiding potential migration of the double-bond. Since this was evidently not the case, it was decided to substitute KO^{t}Bu for other bases to investigate whether elimination could be made to occur without subsequent deprotonation at the 4-position. Attempted dehydrochlorination of **145** using DBU or triethylamine in toluene at 90°C failed and only starting material was recovered in both cases. Due to time restrictions, investigation of further elimination systems unfortunately could not

be conducted although it was apparent from the above observations that a more labile leaving group would be required (allowing the use of a milder base) if elimination to **141** was to be achieved without subsequent rearrangement to **146**.

Based on the above findings, a modified synthetic pathway which may afford greater success was envisaged as the subject of a future study (Scheme 53). The route begins as before with alkene **143**, constructed by reaction of 4-methoxybenzylmagnesium chloride with 1-bromo-3-methylbut-2-ene. Whereas previously **143** had been treated with trichloroisocyanuric acid in the presence of water to furnish chlorohydrin **144**, it was proposed instead to subject the alkene moiety of **143** to dihydroxylation to afford intermediate **147**. A large number of methods are available to effect this transformation and since a *cis* orientation of the hydroxyl groups is not required, the need for highly toxic and expensive osmium reagents is eliminated. The use of potassium permanganate under basic conditions often affords high yields of the corresponding diol[182], although the method of Usui *et al.*[183] utilising Nafion NR50 beads with hydrogen peroxide is considerably more environmentally friendly and excellent results are reported for a range of substrates. One difficulty with the use of Nafion beads in the latter case is that the acidic groups may promote immediate cyclisation to **148** in the manner observed during silica gel chromatography of chlorohydrin **144**; it is possible, however, that a one-pot procedure could be easily devised to directly transform alkene **143** to tetralol **148**.



Scheme 53 (Alternative synthetic route to alkene **141**)

The single hydroxyl group of cyclised **148**, obtained either directly from **143** or by the silica gel-mediated cyclodehydration method applied previously, may then be reacted with an appropriate aromatic sulfonyl chloride to enhance its ability as a leaving group. As tosylated alcohols still require relatively strong bases (KO^tBu etc.) to eliminate them to their respective alkenes[97], it was envisaged that a more efficient leaving group such as a nosylate or triflate would be required to enable elimination to be achieved under milder conditions so as to avert rearrangement of **141** to the conjugated alkene **146**. Since a reasonably large number of such activating sulfonyl reagents are available commercially, this step would require some investigation to determine which leaving group affords the optimum balance between elimination efficacy, economy of the reagent and experimental convenience (*i.e.* air-sensitivity, toxicity, etc.). In an optimum procedure, activation and elimination of the hydroxyl group of **148** would be performed in a one-pot manner in the presence of excess base to yield **141**.

Although the desired alkene **141** has yet to be successfully prepared, the rapidity, convenience and relative safety of the routes discussed provides much support for the further investigation of synthetic pathways to this potentially very useful intermediate.

CHAPTER 6
PHARMACOLOGICAL EVALUATION

6.1 Introduction

The purified ligands synthesised in Chapters 2, 3 and 4 were submitted for binding and functional assays (as the corresponding HCl salts) in order to assess affinity and agonist/antagonist activity at μ, δ and κ opioid receptors. The pharmacological evaluation of all ligands was performed by NIDA-OTDP through a contract to SRI according to the protocols described in Chapter 7. At the time of submission of this thesis, only pharmacological data relating to 9 of the 15 compounds submitted for assay was available.

In the early years of opioid research, pharmacological characterisation of compounds was normally limited to *in vivo* antinociceptive methods. This typically involved subjecting an animal to thermal, mechanical or electrical stimuli in the presence and absence of the test compound in order to determine its antinociceptive potency relative to existing narcotic drugs such as morphine[184]. Further development led to *in vitro* methods of evaluation which, when used in conjunction with tissue containing a homogenous population of a particular receptor type, provide a far more convenient and informative approach to initial ligand characterisation.

6.2 Methods of *in vitro* pharmacological evaluation

6.2.1 Radioligand binding assays

The affinity of a given ligand for μ, δ and κ opioid receptors may be assessed by the use of tritiated versions of the selective agonists DAMGO (μ), Cl-DPDPE (δ) and U69,593 (κ).[94] The usual approach is to incubate samples of the membrane (in this case prepared from cloned human opioid receptors transfected into chinese hamster ovary cells) bearing a population of the desired receptor with the tritiated agonist and various concentrations of the test ligand until equilibrium is reached. The membrane is then separated and its radioactive content measured by scintillation, enabling the IC_{50} value (concentration of unlabelled test ligand required to displace 50% of the tritiated selective agonist from the receptor) and dissociation constant (K_i) to be calculated.

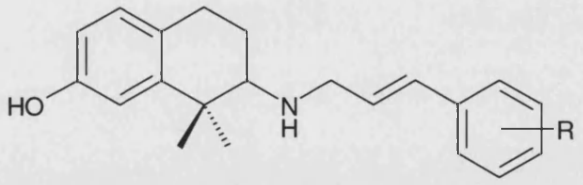
6.2.2 [^{35}S]GTPγS-binding functional assays

The binding of the GTP analogue guanosine-5'-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) to cloned human opioid receptors stimulated by a given ligand provides a means by which agonist activity may be measured.[94] Membrane samples are incubated with [^{35}S]GTPγS, GDP and the test compound. The resulting radioactivity of the separated membrane is determined as for the binding assay, enabling a dose-response curve for the test ligand to be created. A dose-response curve utilising a prototypical full agonist (DAMGO, Cl-DPDPE and U69,593 for μ, δ and κ respectively) is also obtained in order to measure % maximal stimulation and identify partial agonists.

High affinity ligands (with K_i < 200 nM) exhibiting no agonist activity were subsequently tested as antagonists. In this assay, dose-response curves are obtained in the presence of a prototypical full agonist and at least three concentrations of the test ligand. A statistical analysis is conducted and the equilibrium dissociation constant (K_e) calculated which represents the antagonist potency of the test ligand in question.

6.3 Results of pharmacological assays

6.3.1 Ring-substituted N-cinnamyl derivatives



		K_i ± SEM (nM)			Selectivity	
No	**R**	**μ [^{3}H] DAMGO**	**δ [^{3}H] Cl-DPDPE**	**κ [^{3}H] U69,593**	**μ/κ**	**δ/κ**
28	*o*-NH_2	14.8 ± 0.35	1710 ± 399	35.9 ± 9.93	0.4	48
29	*m*-NH_2	48.7 ± 2.65	874 ± 120	339 ± 14.5	0.1	2.6
30	*p*-NH_2	13.8 ± 3.41	880 ± 77.6	78.0 ± 12.2	0.2	11
59	*o*-NO_2	41.0 ± 5.68	608 ± 145	36.1 ± 5.87	1.1	17
62	*o*-NH_2*	26.1 ± 0.19	3480 ± 652	64.0 ± 12.0	0.4	54
26	H	10.7 ± 2.73	472 ± 108	82.3 ± 18.0	0.1	5.7

*with double-bond hydrogenated

Table 14 (Binding assay results for aromatic substituted derivatives of **26**)

No	R	$K_e \pm$ SEM (nM)			Selectivity
		μ vs DAMGO	δ vs Cl-DPDPE	κ vs U69,593	μ/κ
28	*o*-NH_2	5.24 ± 0.61	NT	9.03 ± 0.25	0.6
29	*m*-NH_2	72.9 ± 12.6	NT	NT	-
30	*p*-NH_2	35.6 ± 2.08	NT	89.7 ± 4.35	0.6
59	*o*-NO_2	255 ± 49.9	NT	15.5 ± 0.47	16
62	*o*-NH_2*	16.5 ± 1.03	NT	29.7 ± 1.05	0.6
26	H	67.7 ± 7.59	NT	42.7 ± 2.75	1.6

*with double-bond hydrogenated; NT = not tested

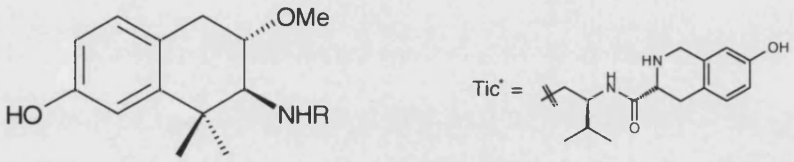
Table 15 (Functional assay results for aromatic substituted derivatives of **26**)

Tables 14 and 15 show the binding and functional assay results obtained for the aromatic substituted derivatives of 3-unsubstituted cinnamyl ligand **26** described in Chapter 2. Analysis of the binding assay results reveals that whilst none of the ligands exhibit markedly superior μ/κ selectivity to **26**, both the *ortho*-NH_2 compound **28** and the *ortho*-NO_2 compound **59** both show an approximately two-fold improvement in κ receptor affinity. It was discussed in Chapter 2 that the design of this series of ligands was based on the findings of Portoghese *et al.*[10,48,51] who elucidated that a correctly positioned basic nitrogen centre was crucial in conferring κ-selectivity to norBNI (**10**) and GNTI (**11**). Whilst the increase in κ affinity for *ortho*-NH_2 derivative **28** may be explained using this concept, the observed κ affinity of *ortho*-NO_2 ligand **59** is entirely unexpected. Hydrogenation of the alkene moiety of **28** to afford **62** appeared to result in a loss in κ affinity, though the relatively high δ/κ selectivity is retained. The *meta*-NH_2 compound **29** was notable due to its low affinity for all but the μ receptor.

The functional assay results in Table 15 confirm the previous finding that *N*-substituted derivatives of the aminotetralin scaffold behave as pure opioid antagonists. The *ortho*-NH_2 ligand **28** was found to be a moderately potent μ and κ antagonist, displaying increased potency relative to unsubstituted **26**. Although saturated derivative **62** exhibited almost identical κ affinity to **28** in the binding assay, it was subsequently found to be a 3-fold less potent κ antagonist in the functional assay. The *ortho*-NO_2 ligand **59** again afforded the most surprising results: although **59** displayed unexpected κ affinity in the binding assay, its μ/κ selectivity was only marginally superior to the other ligands and certainly of no pharmacological significance. When subjected to the functional assay, however, **59**

was found to be not only a moderately potent κ antagonist but possessed a 16-fold greater μ/κ selectivity than was apparent in the binding assay. It is at present unclear why the *ortho*-NO_2 ligand **59** should possess such significant κ affinity and selectivity, though the complete absence of basicity in the nitro group suggests a rather different mode of receptor interaction than the basic nitrogen/Glu297 model proposed by Portoghese.[10,52] It would be of interest to determine whether it is the highly polar nature of the nitro group or its electron withdrawing ability that contributes most to the observed activity.

6.3.2 3-Methoxy derivatives



		$K_i \pm$ SEM (nM)			Selectivity	
No	**R**	**μ [^{3}H] DAMGO**	**δ [^{3}H] Cl-DPDPE**	**κ [^{3}H] U69,593**	**μ/κ**	**δ/κ**
65	H	17.5 ± 5.90	2430 ± 422	149 ± 2.15	0.1	16
74	Cinnamyl	1.63 ± 0.58	22.4 ± 6.70	7.50 ± 0.84	0.2	8.0
76	Allyl	2.3 ± 0.15	1000 ± 89.8	17.2 ± 2.18	0.1	58
66	Tic*	365 ± 4.04	1970 ± 241	3.77 ± 0.02	97	520
26		10.7 ± 2.73	472 ± 108	82.3 ± 18.0	0.1	5.7
R = Tic* (**27**)		23.0 ± 2.75	139 ± 52.1	5.04 ± 0.60	4.6	28

Table 16 (Binding assay results for 3-methoxy ligands)

		$K_e \pm$ SEM (nM)			Selectivity	
No	**R**	**μ vs DAMGO**	**δ vs Cl-DPDPE**	**κ vs U69,593**	**μ/κ**	**δ/κ**
65	H	Agonist**	NT	49.3 ± 4.3	-	-
74	Cinnamyl	2.62 ± 0.40	26.3 ± 3.90	2.12 ± 0.11	1.2	12
76	Allyl	1.69 ± 0.13	NT	2.91 ± 0.29	0.6	-
66	Tic*	NT	NT	15.6 ± 1.28	-	-
26		67.7 ± 7.59	NT	42.7 ± 2.75	1.6	-
R = Tic* (**27**)		139 ± 31.7	503 ± 120	3.04 ± 0.18	46	165

** EC_{50} = 234 ± 55, 31.6% stimulation relative to DAMGO

Table 17 (Functional assay results for 3-methoxy ligands)

The binding profile for the μ-selective *N*-unsubstituted aminotetralin **65** (Table 16) is in general agreement with that previously reported for this compound by Roy *et al.*[126], although in the present assay **65** displayed an approximately 10-fold lower affinity for the μ receptor (it is notable that the details of the assay used by the original authors were not disclosed). Comparison of the results obtained for the *N*-cinnamyl ligand **74** to 3-unsubstituted analogue **26** reveals that the 3-methoxy group exerts a considerable effect on the receptor affinity of this ligand: addition of a 3-methoxy moiety orientated *trans* to the *N*-cinnamyl group significantly increases affinity for all three receptors. Receptor selectivity remains relatively unchanged between the two compounds, with a slight increase in δ/κ selectivity. The ability of the 3-methoxy group to increase affinity is further illustrated by *N*-allyl derivative **76**. In the preliminary 3-unsubstituted series, the *N*-allyl compound displayed only weak affinity for μ receptors (K_i = 202 ± 0.92 nM) and moderate affinity for κ receptors (K_i = 63.7 ± 6.60 nM). Addition of the 3-methoxy moiety has increased μ binding 88-fold and κ binding almost 4-fold, with **76** displaying a preference for the μ receptor. The most considerable gain in selectivity was observed in the JDTic-analogue **66**. Although the ligand did not exhibit increased affinity for receptors other than κ, the loss in affinity at μ and δ has translated into a far more desirable increase in κ receptor selectivity. The new 3-methoxy ligand **66** displays a 97- and 520-fold preference for the κ receptor over the μ and δ receptors respectively.

The functional assay results (Table 17) confirm the findings of Roy *et al.*[126] that **65** behaves as an agonist at the μ receptor, although of lower potency than suggested in the original publication; interestingly, the ligand was also found to moderately antagonise κ receptors. As predicted by the binding results, *N*-cinnamyl ligand **74** was found to be a potent μ and κ antagonist with only moderate affinity for the δ receptor. Of equal significance is the finding that *N*-allyl compound **76** is also a potent μ and κ antagonist, placing this side-chain alongside cinnamyl in its ability to confer antagonist potency. It will be of interest to compare the results of **76** with those of *N*-CPM analogue **75** when available, as the *N*-allyl and *N*-CPM groups mediate similar antagonist activity in the morphinan and related series.

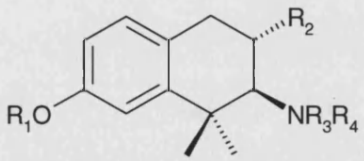
In marked contrast to the binding assay, JDTic-like ligand **66** exhibited a somewhat disappointing κ antagonist activity in the functional assay, being 5-fold less potent than the analogous ligand **27** lacking a 3-methoxy group. Nonetheless,

the high selectivity of **27** for the κ receptor justifies further pharmacological investigation of this interesting ligand and it is intended that *in vivo* studies will be conducted in the near future.

6.4 Concluding remarks

The above pharmacological results confirm the ability of suitable aminotetralin structures to function as 'message' scaffolds in the development of short-acting pure opioid antagonist ligands and provide much scope for further investigation. The unexpected finding that the *ortho*-NO_2 analogue **59** is a moderately potent and selective κ antagonist justifies the further exploration of this side-chain as a κ 'address' and the synthesis of other non-basic *ortho* analogues of **26**. The considerable pharmacological effects exerted by the presence of a 3-methoxy group also warrant further investigation of this structural feature: one particularly interesting possibility would be to synthesise the corresponding 3-methoxy substituted analogue of **59** to observe the effect on κ affinity and selectivity. The exploration of other 3-substituted aminotetralin scaffolds is currently underway (including the vicinal diamines discussed in Chapter 4) which will provide further information on the structure-activity relationships in this series and may yet yield ligands with superior pharmacological profiles to those already disclosed.

At the time of submission, the binding and functional assay results for 9 of the 15 ligands synthesised were available. The pharmacological evaluation of the remaining 6 compounds (Table 18) is expected to be completed in the near future.



No	R_1	R_2	R_3	R_4
75	H	OMe	H	CPM
77	H	OMe	Allyl	Allyl
78	H	OMe	H	n-Propyl
79	H	OMe	H	n-Propylphenyl
92	H	$N(CH_2)_4$	H	Cinnamyl
129	Me	$N(CH_2)_4$	H	Cinnamyl

Table 18 (Ligands submitted for pharmacological testing but data currently unavailable)

CHAPTER 7
EXPERIMENTAL

7.1 Pharmacological methods

Binding and functional *in vitro* assays were carried out by the National Institute on Drug Abuse (NIDA) at Stanford Research Institute, California, USA[94]. The procedures described below were those used to obtain all pharmacological results quoted in this thesis. Compounds selected for *in vitro* testing were converted to their corresponding HCl salts by dissolving the free base in a 5 to 6N solution of HCl in propan-2-ol, followed by carefully evaporation of the solvent *in vacuo*. The resulting salt was thoroughly dried in a vacuum desiccator prior to submission to NIDA.

7.1.1 Radioligand binding assays

Receptor binding studies were conducted on human opioid receptors transfected into Chinese hamster ovary (CHO) cells. The μ cell line was maintained in Ham's F-12 medium supplemented with 10% foetal bovine serum and 400 μg/ml Geneticin (G418). The δ and κ cell lines were maintained in Dulbecco's minimal essential medium (DMEM) supplemented with 10% foetal bovine serum, 400 μg/ml G418 and 0.1% penicillin/streptomycin. All cell lines were grown to full confluence, then harvested for membrane preparation. The membrane used for binding assays was prepared in 50 mM Tris buffer, pH 7.7. Cells were harvested by scraping the plates with a rubber policeman and centrifuged at 500 × g for 10 minutes. The cell pellet was subsequently homogenised in buffer with a polytron, centrifuged at 20,000 × g for 20 minutes, washed and recentrifuged before resuspending at 3 mg protein/mL in buffer to determine protein content. The homogenate was stored at -70°C in 1 mL aliquots.

Routine binding assays were conducted using the prototypical agonist ligands [^{3}H]DAMGO, [^{3}H]Cl-DPDPE and [^{3}H]U69,593 for μ, δ and κ receptors respectively. The assay was performed in triplicate in a 96-well plate. Non-specific binding was measured using 1.0 μM of the unlabelled counterpart of each radioligand. Cell membranes were incubated with the appropriate radioligand and unlabelled test compound for 1 hour at 25°C. For routine experiments, membranes were incubated

with the test compounds at concentrations ranging from 10^{-5} to 10^{-10} M, after which the samples were filtered through glass fibre filters using a Tomtec cell harvester. Filters were dried overnight and bagged with 10 ml scintillation cocktail before counting for 2 minutes on a Wallac Betaplate 1205 liquid scintillation counter

Full characterisation of compounds includes analysis of the data for IC_{50} values and Hill coefficients using the program PRISM. K_i values were calculated using the Cheng-Prusoff transformation:

$$K_i = \frac{IC_{50}}{1+(L/K_d)}$$

where L is the radioligand concentration and K_d the binding affinity of the radioligand as determined previously by saturation analysis.

7.1.2 [^{35}S]GTPγS-binding functional assays

Compounds having K_i values of 200 nM or better in the binding assay were evaluated for agonist/antagonist activity. The membrane was prepared as described for the radioligand binding assay above with the exception that buffer A (20 mM HEPES, 10 mM $MgCl_2$ and 100 mM NaCl at pH 7.4) was used instead of 50 mM Tris buffer. The membrane was incubated with [^{35}S]GTPγS (50 pM), GDP (usually 10μM) and the test compound in a total volume of 200 μL for 60 minutes at 25°C. Samples were subsequently filtered through glass fibre filters and counted as before. A dose-response curve with a prototypical full agonist (DAMGO, Cl-DPDPE and U69,593 for μ, δ and κ receptors respectively) was conducted in each experiment to identify full and partial agonist compounds.

High affinity compounds (K_i < 200 nM) that demonstrated no agonist activity were tested as antagonists. For each test compound, a Schild analysis was conducted utilising a full agonist dose-response curve in the presence of at least three concentrations of the antagonist. pA_2 values and Schild slopes were determined using a statistical program designed for these experiments. The equilibrium dissociation constant, K_e, was calculated as follows:

$$K_e = \frac{a}{DR-1}$$

where a is the nanomolar concentration of the antagonist and DR the shift of the agonist concentration-response curve in the presence of a given concentration of antagonist.

7.2 Analytical specifications

All chemicals were purchased from Aldrich, Acros, Fluka, Avocado or Lancaster chemical companies. The majority of solvents were GPR grade obtained from Fisher Scientific and were used without further purification. Where "anhydrous" is specified in the experimental text, this refers to the "absolute" form of the solvent over molecular sieves available from Fluka.

Column chromatography was performed under gravity using silica gel 60 (35-70 μm) purchased from Merck. Thin layer chromatography for analytical purposes was carried out using aluminium-backed plates coated with silica gel 60 F_{254} purchased from Merck. The chromatograms were visualised using UV light, iodine, ninhydrin, phosphomolybdic acid, 2,4-dinitrophenylhydrazine and potassium permanganate stains.

^1H and ^{13}C NMR spectra were recorded using either a JEOL GX 270 (operating at 270 MHz for ^1H and 70 MHz for ^{13}C) or a JEOL EX 400 (operating at 400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. Chemical shifts are expressed in ppm and spectra were referenced using tetramethylsilane or residual solvent. Coupling constants (J) are reported in Hz and the multiplicities abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), m (multiplet) and br (broad). The abbreviations Ar-CH and Ar-C appearing in the ^{13}C data refer to either aromatic carbon atoms or alkene carbon atoms conjugated with an aromatic group. All mass spectrometry was carried out by the University of Bath Mass Spectrometry Service. High and low resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument with a matrix of *m*-nitrobenzylalcohol. High and low resolution electron impact (EI) mass spectra were obtained using EI ionisation at 70 eV on a VG AutoSpec Q instrument equipped with a Fisons autosampler. Microanalyses were performed with a Perkin-Elmer 240C analysis by the Microanalysis Laboratory, Department of Chemistry,

University of Bath. Melting points were obtained using a Gallenkamp MFB-595 melting point apparatus or a Reichert-Jung hot stage microscope apparatus and are uncorrected.

7.3 Synthetic procedures

2-Amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (23) - Method **A**

Methyl ether **38** (1.04 g, 5.04 mmol) was dissolved in aq. 48% hydrobromic acid (10 ml) and the reaction heated to reflux for 3 hours. The mixture was allowed to cool to RT and the solvent cautiously evaporated *in vacuo* to leave the crude phenol hydrobromide. Water (15 ml) was added and the solution basified to pH 10 with conc. NH_4OH. The resulting emulsion was extracted with $CHCl_3$ (3 × 40 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (1-5% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a brown oil (0.47 g, 49%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH) 0.31; δ_H (270 MHz, $CDCl_3$): 1.21 (3H, s, *gem*-**CH**$_3$), 1.30 (3H, s, *gem*-**CH**$_3$), 1.68-1.82 (1H, m, 3-**CH**), 1.95 (1H, dtd, J = 12.9, 6.4, 3.0, 3-**CH**), 2.80 (2H, m, 2-**CH** + 4-**CH**), 2.87 (1H, m, 4-**CH**), 6.57 (1H, dd, J = 8.4, 2.7, 6-Ar**H**), 6.80 (1H, d, J = 2.7, 8-Ar**H**), 6.91 (1H, d, J = 8.4, 5-Ar**H**); δ_C (70 MHz; $CDCl_3$): 25.68, 27.08, 27.68, 30.08, 39.27, 56.76, 113.93 (Ar-CH), 114.06 (Ar-CH), 126.35 (Ar-C), 130.21 (Ar-CH), 146.05 (Ar-C), 155.00 (Ar-C); EI MS *m/z* 191 (M^+, 40%)

2-Amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (23) - Method **B**

To a stirred solution of methyl ether **38** (0.52 g, 2.52 mmol) in CH_2Cl_2 (15 ml) at -78°C under an atmosphere of nitrogen was added boron tribromide (5.0 ml, 1.0M solution in CH_2Cl_2, 5.00 mmol) dropwise over 30 minutes *via* a syringe. When the addition was complete, the cooling bath was removed and the reaction was stirred for 15 hours. After this time the reaction was quenched by the dropwise addition of MeOH (15 ml). The solvent was evaporated *in vacuo* and the residue redissolved in MeOH (30 ml). After stirring for 15 minutes, the solvent was again evaporated and the residue basified to pH 10 with conc. NH_4OH. Water (10 ml) was added and the emulsion extracted with 3:1 $CHCl_3$: EtOH (3 × 15 ml). The combined organic extracts were washed with water (40 ml), dried ($MgSO_4$), filtered and concentrated *in*

vacuo. Column chromatography (8% MeOH: 91% CH_2Cl_2: 1% NH_4OH) afforded the title product as a brown oil (0.31 g, 64%). See Method A for data.

2-{[(*E*)-3-(2-Aminophenyl)prop-2-enyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (28)

To a stirred solution of **39** (0.32 g, 0.91 mmol) in MeOH (20 ml) at RT was added aq. 7M NH_4OH (18 ml) and iron (II) sulfate heptahydrate (2.27 g, 8.17 mmol). The reaction was heated to reflux for 2 hours after which time the mixture was cooled and suction filtered. The filter pad was washed with $CHCl_3$ (30 ml) and the filtrate adjusted to pH 7 with aq. sat. NH_4Cl. The resulting two-phase system was separated and the aqueous layer extracted with $CHCl_3$ (3 × 40 ml). The combined organic extracts were washed with water (2 × 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a red oil. Column chromatography (3% MeOH: 96% CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow foam (0.19g, 66%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.20; ν_{max} (film) 3220 (br, O-H), 1613 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.24 (3H, s, *gem*-CH_3), 1.36 (3H, s, *gem*-CH_3), 1.71-1.80 (1H, m, 3-C**H**), 2.05-2.11 (1H, m, 3-C**H**), 2.65 (1H, dd, *J* = 9.6, 2.4, 2-C**H**), 2.72 (1H, ddd, *J* = 16.4, 9.2, 5.6, 4-C**H**), 2.83 (1H, dt, *J* = 16.4, 5.6, 4-C**H**), 3.41 (1H, ddd, *J* = 14.4, 7.2, 1.6, NHC**H**$_2$CH), 3.66 (1H, ddd, *J* = 14.4, 6.0, 1.6, NHC**H**$_2$CH), 6.18 (1H, dt, *J* = 15.6, 6.8, CH_2C**H**=CH), 6.56 (1H, dd, *J* = 8.4, 2.8, 6-Ar**H**), 6.59 (1H, d, *J* = 15.2, CH_2CH=C**H**), 6.68 (1H, dd, *J* = 8.4, 1.2, Ar-**H**[*o*-NH_2]), 6.72 (1H, dd, *J* = 7.6, 0.8, Ar-**H**[*p*-NH_2]), 6.77 (1H, d, *J* = 2.8, 8-Ar**H**), 6.89 (1H, d, *J* = 8.4, 5-Ar**H**), 7.06 (1H, td, *J* = 7.6, 1.6, Ar-**H**[*p*-CH=CH]), 7.23 (1H, dd, *J* = 7.6, 1.6, Ar-**H**[*o*-CH=CH]); δ_C (100 MHz; $CDCl_3$): 24.06, 26.10, 27.92, 29.77, 39.10, 50.93, 62.56, 113.50 (Ar-CH), 113.73 (Ar-CH), 116.35 (Ar-CH), 119.30 (Ar-CH), 123.79 (Ar-C), 127.33 (Ar-CH), 127.69 (Ar-CH), 128.59 (Ar-CH), 129.96 (Ar-CH), 130.62 (Ar-CH), 143.58 (Ar-C), 146.95 (2 × Ar-C), 154.09 (Ar-C); EI MS *m/z* 324 (MH^+, 70%); EI MS *m/z* 322 (M^+, 45%); HRMS calc. for $C_{21}H_{26}N_2O$ 322.2045, found 322.2050; CHN calc. for $C_{21}H_{26}N_2O.2HCl$: C 63.8, H 7.14, N 7.09, found: C 63.5, H 7.17, N 7.10

2-{[(*E*)-3-(3-Aminophenyl)prop-2-enyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (29)

The procedure used for the preparation of **28** was employed. Nitro compound **40** (0.12 g, 0.35 mmol) was treated with iron (II) sulfate heptahydrate (0.87 g, 3.12 mmol) in the presence of NH_4OH according to the protocol described. Column chromatography (3% MeOH: 96% CH_2Cl_2: 1% NH_4OH) afforded the title compound as a colourless oil (74 mg, 66%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.15; ν_{max} (film) 3370 (O-H), 1614 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.23 (3H, s, *gem*-CH_3), 1.34 (3H, s, *gem*-CH_3), 1.72-1.83 (1H, m, 3-C**H**), 2.04-2.22 (1H, m, 3-C**H**), 2.67 (1H, dd, *J* = 9.6, 2.8, 2-C**H**), 2.70-2.78 (1H, m, 4-C**H**), 2.83 (1H, dt, *J* = 16.8, 5.6, 4-C**H**), 3.40 (1H, ddd, *J* = 14.0, 7.2, 0.8, NHC**H**$_2$CH), 3.66 (1H, ddd, *J* = 14.0, 5.6, 1.2, NHC**H**$_2$CH), 3.70-4.20 (4H, br-s, O-**H** + N-**H** + N**H**$_2$), 2.90 (1H, ddd, *J* = 15.6, 7.2, 6.0, CH_2C**H**=CH), 6.49 (1H, d, *J* = 15.6, CH_2CH=C**H**), 6.60 (2H, dd, *J* = 8.0, 2.4, 6-Ar**H** + Ar-**H**[*p*-CH=CH]), 6.71 (1H, *pseudo*-t, *J* = 2.0, Ar-**H**[*o*-CH=CH, *o*-NH_2]), 6.78-6.82 (2H, m, 8-Ar**H** + Ar-**H**[*p*-NH_2]), 6.91 (1H, d, *J* = 8.0, 5-Ar**H**), 7.13 (1H, t, *J* = 8.0, Ar-**H**[*m*-NH_2]); δ_C (100 MHz; $CDCl_3$): 23.57, 25.67, 27.53, 29.29, 38.66, 50.27, 62.28, 113.06 (Ar-CH), 113.59 (Ar-CH), 113.73 (Ar-CH), 114.76 (Ar-CH), 117.41 (Ar-CH), 126.63 (Ar-C), 128.26 (Ar-CH), 129.55 (Ar-CH), 129.79 (Ar-CH), 131.97 (Ar-CH), 138.15 (Ar-C), 146.28 (Ar-C), 146.65 (Ar-C), 154.38 (Ar-C); FAB MS *m/z* 323 (MH^+, 100%); HRMS calc. for $C_{21}H_{27}N_2O$ 323.2123, found 323.2125; CHN calc. for $C_{21}H_{26}N_2O.2HCl.CH_3OH.0.5H_2O$: C 60.5, H 7.62, N 6.42, found: C 60.1, H 7.40, N 6.02

2-{[(*E*)-3-(4-Aminophenyl)prop-2-enyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (30)

The procedure used for the preparation of **28** was employed. Nitro compound **41** (0.097 g, 0.28 mmol) was treated with iron (II) sulfate heptahydrate (0.69 g, 2.48 mmol) in the presence of NH_4OH according to the protocol described. Column chromatography (3% MeOH: 96% CH_2Cl_2: 1% NH_4OH) afforded a mixture of the saturated and unsaturated product. Therefore, column chromatography was repeated (1% MeOH: 98% CH_2Cl_2: 1% NH_4OH) to give the pure title compound as a yellow oil (25 mg, 28%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.24; ν_{max} (film) 3368 (O-H), 1609 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.22 (3H, s, *gem*-CH_3), 1.35

(3H, s, *gem*-CH_3), 1.68-1.78 (1H, m, 3-CH), 2.02-2.10 (1H, m, 3-CH), 2.63 (1H, dd, J = 9.2, 2.4, 2-CH), 2.71 (1H, ddd, J = 16.4, 10.0, 6.0, 4-CH), 2.81 (1H, dt, J = 16.4, 5.2, 4-CH), 3.34 (1H, ddd, J = 13.6, 7.2, 0.8, CH_2CH=CH), 3.60 (1H, ddd, J = 13.6, 6.0, 1.2, CH_2CH=CH), 6.12 (1H, dt, J = 15.6, 6.4, CH_2CH=CH), 6.43 (1H, d, J = 15.6, CH_2CH=CH), 6.56 (1H, dd, J = 8.0, 2.8, 6-ArH), 6.62 (2H, d-*pseudo*-t, J = 8.4, 2.0, 2 × Ar-H[*o*-NH_2]), 6.77 (1H, d, J = 2.8, 8-ArH), 6.88 (1H, d, J = 8.0, 5-ArH), 7.17 (2H, d-*pseudo*-t, J = 8.4, 2.0, 2 × Ar-H[*o*-CH=CH]); δ_C (100 MHz; $CDCl_3$): 24.06, 26.07, 27.97, 29.68, 39.09, 50.87, 62.39, 113.38 (Ar-CH), 113.70 (Ar-CH), 115.43 (Ar-CH), 125.27 (Ar-CH), 127.30 (Ar-C), 127.60 (Ar-CH), 128.14 (Ar-C), 129.94 (Ar-CH), 131.52 (Ar-CH), 145.83 (Ar-C), 147.11 (Ar-C), 154.00 (Ar-C); FAB MS *m/z* 323 (MH^+, 35%); HRMS calc. for $C_{21}H_{27}N_2O$ 323.2123, found 323.2112; CHN calc. for $C_{21}H_{26}N_2O.2HCl.1.5H_2O$: C 59.7, H 7.40, N 6.63, found: C 60.0, H 7.46, N 6.23

7-Methoxy-3,4-dihydronaphthalen-2(1*H*)-one (35) - Method **A**

To a stirred refluxing solution of **47** (11.0 g, 59.1 mmol) in EtOH (150 ml) was carefully added freshly cut sodium (13.6 g, 591 mmol) in small pieces at such a rate as to maintain vigorous reflux (30 min). When all the sodium had dissolved, the mixture was cooled to 0°C and 5M HCl (150 ml) was carefully added, causing the colour of the solution to change from colourless to blue to yellow. The reaction was heated to reflux for a further 30 min before allowing to cool to RT. The mixture was then extracted with Et_2O (3 × 120 ml) and the combined organic layers washed with sat. aq. $NaHCO_3$ (100 ml) before removal of the solvent *in vacuo*. The crude ketone was then added to a vigorously stirred mixture of sat. aq. sodium bisulfite (100 ml) and EtOH (70 ml). After 30 min, stirring was stopped and the mixture allowed to stand for a futher 15 min. The white solid which formed was filtered off and washed with Et_2O (3 × 50 ml), before redissolving in H_2O (150 ml). An excess of solid Na_2CO_3 was added with vigorous shaking and the mixture re-extracted with Et_2O (3 × 100 ml). The combined extracts were washed with H_2O (3 × 150 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product as a yellow liquid (6.56 g, 63%); R_f (50% EtOAc : 50% Hexanes): 0.60; ν_{max} (film) 1713 (C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.54 (2H, t, J = 7.0, 3-CH_2), 3.00 (2H, t, J = 7.0, 4-CH_2), 3.56 (2H, s, 1-CH_2), 3.79 (3H, s, 7-OCH_3), 6.68 (1H, d, J = 2.6, 8-ArH),

6.76 (1H, dd, J = 8.4, 2.6, 6-Ar**H**), 7.14 (1H, d, J = 8.4, 5-Ar**H**); δ_C (67.8 MHz; $CDCl_3$) 27.18, 38.28, 44.90, 55.01, 112.02 (Ar-CH), 113.23 (Ar-CH), 128.25 (Ar-CH), 128.48 (Ar-C), 134.27 (Ar-C), 158.27 (Ar-C), 210.29 (C=O); EI MS *m/z* 176 (M^+, 50%)

7-Methoxy-3,4-dihydronaphthalen-2(1*H*)-one (35) - Method **B**

Freshly cut sodium (13.0 g, 565 mmol) in small pieces was added to a solution of **47** (13.3 g, 70.7 mmol) in anhydrous THF (180 ml) contained in a 1L round-bottomed flask at RT - moderate stirring was maintained throughout the addition to avoid clumping. The flask was then fitted with a pressure-equalising dropping funnel charged with EtOH (200 ml) and the system purged with nitrogen. The mixture was cautiously heated to 60°C and the ethanol added with vigorous stirring at such a rate as to maintain reflux (the rate of addition was slow at first as frothing tended to occur but as this subsided the rate was gradually increased – total addition time 45 minutes). When the addition was complete, the reaction was maintained at reflux temperature until all the sodium had reacted. The system was then cooled to 0°C and aq. 5M HCl (150 ml) was added as rapidly as possible (causing a colour change of colourless → blue → yellow), after which the mixture was heated to reflux for a further hour. The reaction was allowed to cool to RT and diethyl ether (400 ml) added. The resulting two-phase system was separated and the aqueous layer extracted with diethyl ether (2 × 200 ml). The combined organic layers were washed with water (2 × 200 ml) and concentrated *in vacuo*. The resulting orange oil was added to a vigorously stirred mixture of aq. sat. sodium metabisulfite (100 ml) and EtOH (70 ml) at 0°C. The mixture was stirred vigorously for 30 minutes then allowed to stand for a further 30 minutes. The bisulfite adduct was subsequently collected by suction filtration and repeatedly washed with diethyl ether until a clean white solid was obtained. The adduct was then dissolved in water (300 ml) and excess sodium carbonate added with vigorous stirring. The mixture was allowed to stir at RT for 30 minutes after which time a yellow oil had separated. The system was extracted with diethyl ether (3 × 150 ml) and the combined organic layers washed with water (3 × 200 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product as a yellow liquid (11.8 g, 95%); See Method A for data.

7-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2(1*H*)-one (36) - Method **A**

To a stirred slurry of sodium hydride (2.61 g, 60 % dispersion in oil, 68.4 mmol) in toluene (100 ml) at 0°C under an atmosphere of nitrogen was added a solution of **36** (4.02 g, 22.7 mmol) in toluene (15 ml) dropwise over 15 minutes *via* a syringe. Iodomethane (4.26 ml, 68.4 mmol) was then added dropwise and the mixture allowed to stir for 15 hours at RT. After this time the reaction was quenched by the cautious addition of sat. aq. NH_4Cl (50 ml). Water (50 ml) was added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 70 ml) and the combined organic layers were washed with 10% sodium bisulfite solution (2 × 80 ml), brine (70 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent *in vacuo* gave a brown oil which was distilled under reduced pressure (b.p. 145-148 °C at 5 mmHg) to afford the title product as a colourless liquid (2.87 g, 62%); R_f (50% EtOAc : 50% Hexanes): 0.73; δ_H (270 MHz; $CDCl_3$): 1.43 (6H, s, 2 × *gem*-CH_3), 2.66 (2H, t, J = 6.4, 3-CH_2), 3.04 (2H, t, J = 6.4, 4-CH_2), 3.82 (3H, s, 7-OCH_3), 6.75 (1H, dd, J = 8.2, 2.7, 6-Ar**H**), 6.88 (1H, d, J = 2.7, 8-Ar**H**), 7.10 (1H, d, J = 8.2, 5-Ar**H**); δ_C (70 MHz; $CDCl_3$): 26.55, 27.49, 37.24, 47.63, 55.01, 111.14 (Ar-CH), 111.96 (Ar-CH), 127.15 (Ar-C), 128.83 (Ar-CH), 144.63 (Ar-C), 158.56 (Ar-C), 214.47 (Ar-C); FAB MS *m/z* 204 (M^+, 100%)

7-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2(1*H*)-one (36) - Method **B**

To a stirred solution of ketone **35** (15.0 g, 85.1 mmol) and iodomethane (13.2 ml, 213 mmol) in anhydrous THF (300 ml) at 0°C was added potassium *tert*-butoxide (26.8 g, 255 mmol) in small portions over 40 minutes. When the addition was complete, the system was purged with nitrogen and stirred at 0°C for 1 hour. The reaction was then allowed to warm to RT and stirred for a further 18 hours. Aq. 2M HCl (100 ml) was added cautiously to quench the reaction and the mixture stirred for 15 minutes. The THF was evaporated *in vacuo* and the resulting emulsion extracted with diethyl ether (3 × 150 ml). The combined organic layers were washed with aq. 2M sodium metabisulfite (200 ml) and water (200 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude dimethylated ketone as a yellow liquid (21.4 g). See Method A for data. The ketone was immediately converted to oxime **37** without further purification.

7-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2(1*H*)-one oxime (37)

To a vigorously stirred solution of hydroxylamine hydrochloride (21.8 g, 314 mmol) and sodium acetate (21.5 g, 262 mmol) in water (80 ml) at RT was added a solution of unpurified dimethylated ketone **36** (21.4 g, 105 mmol) in MeOH (80 ml). The reaction was heated at reflux for 3 hours then cooled to RT and stirred for a further 18 hours. The solid oxime which formed was collected by suction filtration, washed with ice-cold MeOH (2 × 20 ml) and dried in a vacuum desiccator to afford the title product as a white solid (15.0 g, 81% from **35**); R_f (50% EtOAc: 50% Hexanes): 0.59; m.p. 140-142 °C; ν_{max} (KBr) 1628 (C=N), 1386 (*gem*-$(CH_3)_2$) cm^{-1}; δ_H (270 MHz; $CDCl_3$): 1.50 (6H, s, 2 × *gem*-CH_3), 2.79-2.92 (4H, m, 3-CH_2 + 4-CH_2), 3.81 (3H, s, 7-OCH_3), 6.71 (1H, dd, J = 8.4, 2.6, 6-Ar**H**), 6.94 (1H, d, J = 2.6, 8-Ar**H**), 7.06 (1H, d, J = 8.4, 5-Ar**H**), 7.39 (1H, br-s, O-**H**); δ_C (70 MHz; $CDCl_3$): 22.23, 27.05, 27.99, 41.20, 55.41, 111.13 (Ar-CH), 111.51 (Ar-CH), 128.62 (Ar-C), 129.22 (Ar-CH), 145.07 (Ar-C), 158.61 (Ar-C), 165.10 (C=NOH); EI MS *m/z* 219 (M^+, 65%)

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (38) – Method **A**

To a stirred solution of **37** (1.30 g, 5.93 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C was added sodium borohydride (0.90 g, 23.7 mmol). The mixture was stirred at 0°C for 10 minutes under an atmosphere of nitrogen before the dropwise addition of 100% titanium (IV) chloride (1.3 ml, 11.9 mmol) *via* a syringe. The reaction was then heated to reflux for 15 hours after which time the mixture was cooled to 0°C and quenched by the cautious dropwise addition of H_2O (20 ml). The solution was acidifed to pH 4 with aq. 2M HCl and subsequently washed with $CHCl_3$ (3 × 50 ml). The aqueous layer was then basified to pH 10 with conc. NH_4OH and extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were washed with water (2 × 80 ml), brine (70 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product as a colourless oil (0.70 g, 57%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.38; ν_{max} (film) 1610 (N-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.23 (3H, s, *gem*-CH_3), 1.33 (3H, s, *gem*-CH_3), 1.68-1.82 (1H, m, 3-C**H**), 1.94 (1H, dtd, J = 13.2, 7.3, 3.3, 3-C**H**), 2.76-2.85 (2H, m, 2-C**H** + 4-C**H**), 2.88 (1H, m, 4-C**H**), 3.79 (3H, s, 7-OCH_3), 6.68 (1H, dd, J = 8.4, 2.6, 6-Ar**H**), 6.89 (1H, d, J = 2.6, 8-

ArH), 6.99 (1H, d, J = 8.4, 5-ArH); δ_C (70 MHz; $CDCl_3$): 24.85, 26.65, 27.57, 29.17, 38.74, 55.03, 56.04, 111.00 (Ar-CH), 112.34 (Ar-CH), 126.89 (Ar-C), 129.52 (Ar-CH), 146.00 (Ar-C), 157.71 (Ar-C); EI MS m/z (M^+, 100%)

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (38) – Method **B**

To a stirred solution of zirconium (IV) chloride (0.72 g, 3.09 mmol) in anhydrous 1,2-dimethoxyethane (20 ml) at RT was added sodium borohydride (0.37 g, 9.86 mmol) in small portions over 5 minutes. The flask was fitted with a pressure-equalising dropping funnel containing a solution of oxime **37** (0.54 g, 2.46 mmol) in anhydrous 1,2-dimethoxyethane (10 ml) and the system purged with nitrogen. The mixture was stirred for 10 minutes until the effervescence had subsided, after which the oxime solution was added in a dropwise fashion over 15 minutes. When the addition was complete, the reaction was heated to gentle reflux for 24 hours then allowed to cool to RT. An excess of sodium sulfate decahydrate was added (until a granular precipitate was obtained) to quench the reaction and the inorganic salts separated by suction filtration. The filter pad was washed with 1,2-dimethoxyethane (2 × 15 ml) and the filtrate concentrated *in vacuo*. The residue was redissolved in 5M HCl in propan-2-ol (20 ml) and the solvent subsequently removed *in vacuo* to afford the amine hydrochloride as white crystals which were washed with EtOAc (2 × 15 ml) and dried in a vacuum desiccator (0.41 g, 68%). The free base was obtained by treating the hydrochloride with conc. NH_4OH and extracting with $CHCl_3$. See Method A for data.

2,7-Dimethoxynaphthalene (47) - Method **A**

To a stirred suspension of sodium hydride (15.0 g, 60% dispersion in mineral oil, 375 mmol) in anhydrous DMF (200 ml) at 0°C under an atmosphere of nitrogen was added a solution of 2,7-dihydroxynaphthalene (15.0 g, 93.7 mmol) in anhydrous DMF (60 ml) dropwise *via* syringe. The mixture was stirred at 0°C for 10 minutes before the dropwise addition of iodomethane (17.5 ml, 281 mmol), after which the reaction was allowed to warm to RT and stirred for 18 hours. The mixture was quenched by the very cautious (HIGHLY EXOTHERMIC!) addition of water (150 ml) to the reaction mixture at 0°C. The resulting precipitate of 2,7-dimethoxynaphthalene was collected by suction filtration, washed with water (2 × 50

ml) and dried overnight in a vacuum desiccator to give the title product as light pink crystals (15.1 g, 87%); R_f (50% EtOAc: 50% hexane): 0.71; m.p. 136-138 °C (Lit. 138 °C); ν_{max} (KBr) 3058 (aromatic C-H), 2834 (OC-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 3.91 (6H, s, 7-OCH_3), 7.00 (2H, dd, *J* = 8.8, 2.6, 3-Ar**H** + 6-Ar**H**), 7.06 (2H, d, *J* = 2.6, 1-Ar**H** + 8-Ar**H**), 7.66 (2H, d, *J* = 8.8, 4-Ar**H** + 5-Ar**H**); δ_C (70 MHz; $CDCl_3$): 55.24 (2 × OCH_3), 105.22 (Ar-C), 115.99 (Ar-CH), 124.23 (Ar-C), 129.12 (Ar-CH), 135.89 (Ar-C), 158.04 (Ar-C); EI MS *m/z* 188 (MH^+,100%)

2,7-Dimethoxynaphthalene (47) - Method B

To a vigorously stirred solution of 2,7-dihydroxynaphthalene (23.1 g, 144 mmol) in acetone (350 ml) at RT was added powdered potassium carbonate (59.8 g, 433 mmol). The mixture was stirred for 5 minutes before dimethyl sulfate (41.0 ml, 433 mmol) was added rapidly. The reaction was subsequently heated to reflux for 4 hours then allowed to cool to RT. Aq. 4M KOH (300 ml) was cautiously added and the mixture stirred at RT for 30 minutes, after which time the acetone was evaporated *in vacuo* causing 2,7-dimethoxynaphthalene to precipitate out. The product was collected by suction filtration, washed with water (3 × 50 ml) and dried over phosphorus pentoxide to afford the title product as light brown crystals (22.0 g, 81%). See Method A for data.

3-(3-Nitrophenyl)acrylaldehyde (58)

To a stirred suspension of 3-nitrobenzaldehyde (5.00 g, 33.1 mmol) in acetaldehyde (15 ml) at 0°C was added a 25% solution of potassium hydroxide in MeOH dropwise until the solid dissolved. Acetic anhydride (25 ml) was added and the mixture heated at reflux for 1 hour. The reaction was then allowed to cool to RT before pouring into water (50 ml). The mixture was acidified by the addition of aq. 5M HCl (20 ml) and heated to reflux for a further 45 minutes, after which the flask was cooled in ice. The crystals which formed were collected by suction filtration and subsequently recrystallised from EtOH to afford the title product as fine yellow-brown crystals (1.81 g, 31%); R_f (40% CH_2Cl_2: 60% Hexanes): 0.34; ν_{max} (KBr) 1678 (unsat. C=O), 1524 and 1354 (N=O) cm^{-1}, δ_H (270 MHz, $CDCl_3$): 6.81 (1H, dd, *J* = 16.1, 7.4, CH=C**H**COH), 7.53 (1H, d, *J* = 16.1, ArC**H**=CHCOH), 7.64 (1H, t, *J* = 7.9, Ar-**H**[*o*-NO_2]), 7.88 (1H, d, *J* = 7.9, Ar-**H**[*p*-NO_2]), 8.28 (1H, ddd, *J* = 8.2, 2.2,

1.0, Ar-**H**[*p*-CH=CH]), 8.41 (1H, *pseudo*-t, *J* = 1.8, Ar-**H**[*o*-NO_2 + *o*-CH=CH]), 9.76 (1H, d, *J* = 7.4, CO**H**); δ_C (70 MHz; $CDCl_3$): 123.11, 125.37, 130.93, 133.64, 148.80, 149.13, 192.93; FAB MS *m/z* 178 (MH^+, 65%)

1,1-Dimethyl-2-{[(*E*)-3-(2-nitrophenyl)allyl]amino}-1,2,3,4-tetrahydro naphthalen-7-ol (59)

To a stirred solution of **23** (0.21 g, 1.09 mmol) in anhydrous CH_2Cl_2 (10 ml) at RT was added 2-nitrocinnamaldehyde (0.29 g, 1.64 mmol). The reaction was stirred for 15 hours at RT after which time the solvent was removed *in vacuo*. The residue was redissolved in anhydrous MeOH (20 ml) and the solution cooled to 0°C. Sodium borohydride (0.17 g, 4.37 mmol) was added portionwise over 1 hour and the resulting mixture stirred for a further 15 hours at RT. The reaction was quenched by the dropwise addition of aq. 1M HCl (15 ml) and the solution adjusted to pH 7 with aq. sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 25 ml) and the combined extracts were washed with brine (40 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (30% EtOAc: 70% Hexanes) afforded the title product as a yellow foam (0.32 g, 83%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.40; ν_{max} (film) 3324 (br, O-H), 1523 and 1345 (N=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.22 (3H, s, *gem*-CH_3), 1.35 (3H, s, *gem*-CH_3), 1.62-1.78 (1H, m, 3-C**H**), 2.02-2.12 (1H, m, 3-C**H**), 2.61 (1H, dd, *J* = 9.6, 2.7, 2-C**H**), 2.72-2.81 (2H, m, 4-CH_2), 3.44 (1H, ddd, *J* = 14.2, 6.9, 1.2, NHC**H**$_2$CH), 3.67 (1H, ddd, *J* = 14.2, 5.8, 1.7, NHC**H**$_2$CH), 6.29 (1H, dt, *J* = 15.6, 5.7, CH_2C**H**=CH), 6.56 (1H, dd, *J* = 8.4, 2.6, 6-C**H**), 6.79 (1H, d, *J* = 2.6, 8-C**H**), 6.90 (1H, d, *J* = 8.4, 5-C**H**), 7.02 (1H, d, *J* = 15.6, CH_2CH=C**H**), 7.35 (1H, ddd, *J* = 8.2, 6.9, 2.0, Ar-**H**[*p*-CH=CH]), 7.50-7.58 (2H, m, Ar-**H**[*o*-CH=CH] + Ar-**H**[*p*-NO_2]), 7.89 (1H, dd, *J* = 8.2, 1.2, Ar-**H**[*o*-NO_2]); δ_C (70 MHz; $CDCl_3$): 23.53, 25.64, 27.45, 29.41, 38.82, 50.08, 62.01, 113.14 (Ar-CH), 113.40 (Ar-CH), 124.48 (Ar-CH), 126.34 (Ar-CH), 127.22 (Ar-C), 127.82 (Ar-CH), 128.62 (Ar-CH), 129.79 (Ar-CH), 132.21 (Ar-C), 133.00 (Ar-CH), 134.87 (Ar-CH), 146.96 (Ar-C), 148.18 (Ar-C), 153.85 (Ar-C); FAB MS *m/z* 353 (MH^+, 100%)

1,1-Dimethyl-2-{[(*E*)-3-(3-nitrophenyl)allyl]amino}-1,2,3,4-tetrahydro naphthalen-7-ol (60)

To a stirred solution of **23** (82 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (2 ml) at RT was added aldehyde **58** (91 mg, 0.51 mmol). The reaction was stirred for 17 hours under an atmosphere of nitrogen, during which time a cream precipitate of the imine formed. The solvent was evaporated *in vacuo* and the residue redissolved in 4:1 MeOH: DMF (7 ml) and the solution cooled to 0°C. Sodium borohydride (65 mg, 1.72 mmol) was added portionwise over 1 hour and the resulting mixture stirred for a further 15 hours at RT. The reaction was quenched by the dropwise addition of aq. 1M HCl (15 ml) and the solution adjusted to pH 7 with aq. sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 15 ml) and the combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (30% EtOAc: 70% Hexanes) afforded the title product as a yellow oil (130 mg, 86%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.34; δ_H (270 MHz, $CDCl_3$): 1.22 (3H, s, *gem*-CH_3), 1.35 (3H, s, *gem*-CH_3), 1.64-1.80 (1H, m, 3-C**H**), 2.00-2.12 (1H, m, 3-C**H**), 2.61 (1H, dd, *J* = 9.7, 2.7, 2-C**H**), 2.66-2.88 (2H, m, 4-CH_2), 3.26 (2H, br-s, N-**H** + O-**H**), 3.41 (1H, dd, *J* = 14.6, 6.4, NHC**H**$_2$CH), 3.66 (1H, ddd, *J* = 14.6, 5.4, 1.0, NHC**H**$_2$CH), 6.45 (1H, dt, *J* = 15.8, 5.9, CH_2C**H**=CH), 6.56 (1H, dd, *J* = 8.2, 2.7, 6-C**H**), 6.61 (1H, d, *J* = 15.8, CH_2CH=C**H**), 6.78 (1H, d, *J* = 2.5, 8-C**H**), 6.89 (1H, d, *J* = 8.2, 5-C**H**), 7.44 (1H, t, *J* = 7.9, Ar-**H**[*m*-NO_2]), 7.62 (1H, d, *J* = 7.9, Ar-**H**[*p*-NO_2]), 8.04 (1H, ddd, *J* = 7.9, 2.0, 1.0, Ar-**H**[*p*-CH=CH]), 8.17 (1H, t, *J* = 2.0); FAB MS *m/z* 353 (MH^+, 100%); HRMS calc. for $C_{21}H_{25}N_2O_3$ 353.1865, found 353.1875

1,1-Dimethyl-2-{[(*E*)-3-(4-nitrophenyl)allyl]amino}-1,2,3,4-tetrahydro naphthalen-7-ol (61)

The procedure used for the preparation of *meta*-NO_2 analogue **60** was employed. Aminotetralin **23** (0.14 g, 0.73 mmol) was reacted with 4-nitrocinnamaldehyde (0.16 g, 0.88 mmol) and the resulting imine subsequently treated with sodium borohydride (0.11 g, 2.93 mmol). Column chromatography (1% MeOH: 98% CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow oil (0.21 g, 81%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.44; ν_{max} (film) 3369 (br, O-H), 1514 and 1343 (N=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.25 (3H, s, *gem*-CH_3), 1.38 (3H,

s, *gem*-CH_3), 1.68-1.79 (1H, m, 3-C**H**), 2.03-2.11 (1H, m, 3-C**H**), 2.61 (1H, dd, *J* = 9.6, 2.8, 2-C**H**), 2.73 (1H, ddd, *J* = 15.6, 9.2, 5.6, 4-C**H**), 2.83 (1H, dt, *J* = 15.6, 5.6, 4-C**H**), 3.44 (1H, ddd, *J* = 14.4, 6.4, 1.2, NHCH_2CH), 3.69 (1H, ddd, *J* = 14.4, 5.6, 1.2, NHCH_2CH), 6.52 (1H, dt, *J* = 16.0, 6.4, CH_2C**H**=CH), 6.58 (1H, dd, *J* = 8.4, 2.8, 6-C**H**), 6.63 (1H, d, *J* = 16.0, CH_2CH=C**H**), 6.80 (1H, d, *J* = 2.0, 8-C**H**), 6.90 (1H, d, *J* = 8.4, 5-C**H**), 7.47 (2H, d-*pseudo*-t, *J* = 8.8, 1.6, 2 × Ar-**H**[*o*-CH=CH]), 8.15 (2H, d-*pseudo*-t, *J* = 8.8, 1.6, 2 × Ar-**H**[*o*-NO_2]); δ_C (100 MHz; $CDCl_3$): 24.06, 26.08, 27.84, 29.83, 39.19, 50.44, 62.67, 113.35 (Ar-CH), 113.60 (Ar-CH), 124.21 (Ar-CH), 126.90 (Ar-CH), 127.27 (Ar-C), 129.12 (Ar-CH), 129.99 (Ar-CH), 134.71 (Ar-CH), 143.87 (Ar-C), 146.85 (Ar-C), 147.01 (Ar-C), 153.91 (Ar-C); FAB MS *m/z* 353 (MH^+, 45%); HRMS calc. for $C_{21}H_{25}N_2O_3$ 353.1865, found 353.1883

2-{[3-(2-Aminophenyl)propyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (62)

To a vigorously stirred solution of **59** (0.20 g, 0.57 mmol) in EtOH (25 ml) at RT was added Raney nickel (1 spatula). The mixture was stirred for 5 minutes before the dropwise addition of hydrazine hydrate (0.18 ml, 5.67 mmol). Stirring was continued for 15 hours at RT after which time the reaction mixture was filtered carefully through Celite® (ensuring that the catalyst remained moist at all times). The filter pad was washed with EtOH (50 ml) and the filtrate evaporated *in vacuo*. Column chromatography (6% MeOH: 93 %DCM: 1% NH_4OH) afforded the title product as a colourless oil (0.15 g, 79%); R_f (10 % MeOH: 89 % DCM: 1 % NH_4OH) 0.26; ν_{max} (film) 1614 (N-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.19 (3H, s, *gem*-CH_3), 1.30 (3H, s, *gem*-CH_3), 1.62-1.75 (1H, m, 3-C**H**), 1.84 (2H, quint., *J* = 6.4, NHCH_2CH_2), 1.97-2.09 (1H, m, 3-C**H**), 2.53-2.67 (5H, m, 2-C**H** + NHCH_2CH_2 + CH_2CH_2Ar), 2.68-2.78 (1H, m, 4-C**H**), 2.80-2.93 (1H, m, 4-C**H**), 4.07 (4H, br s, N-**H** + O-**H** + NH_2), 6.55 (1H, dd, *J* = 8.4, 2.5, 6-Ar**H**), 6.67 (1H, d, *J* = 7.9, Ar-**H**[*o*-NH_2]), 6.73 (1H, d, *J* = 2.5, 8-Ar**H**), 6.76 (1H, d, *J* = 7.4, Ar-**H**[*o*-CH=CH]), 6.87 (1H, d, *J* = 8.4, 5-Ar**H**), 7.00-7.08 (2H, m, Ar-**H**[*p*-CH=CH] + Ar-**H**[*p*-NH_2]); δ_C (70 MHz; $CDCl_3$): 23.11, 25.61, 27.10, 28.23, 29.53, 29.66, 38.51, 46.53, 62.88, 113.37 (Ar-CH), 113.50 (Ar-CH), 115.83 (Ar-CH), 118.90 (Ar-CH), 126.51 (Ar-C), 126.64 (Ar-C), 126.93 (Ar-CH), 129.56 (Ar-CH), 129.70 (Ar-CH), 144.35 (Ar-C), 146.37 (Ar-C), 154.22 (Ar-C); FAB MS *m/z* 325 (MH^+, 100 %); HRMS calc. for $C_{21}H_{29}N_2O$

325.2280, found 325.2269; CHN calc. for $C_{21}H_{23}N_2O.2HCl.1.5H_2O$: C 59.4, H 7.84, N 6.60, found: C 59.3, H 7.53, N 6.53

***trans*-2-Amino-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (65)**

To a stirred solution of **70** (1.11 g, 2.63 mmol) in CH_2Cl_2 (20 ml) at RT was added trifluoroacetic acid (2.92 ml, 39.5 mmol) dropwise. The reaction was stirred for 18 hours then quenched by the dropwise addition of aq. sat. $NaHCO_3$ (20 ml). The aqueous layer was adjusted to pH 10 with conc. NH_4OH and the layers were separated. The aqueous layer was extracted with 3:1 $CHCl_3$: EtOH (2 × 25 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product as an off-white solid (0.58 g, 100%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.15; ν_{max} (film) 3294 (O-H), 1582 (N-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.15 (3H, s, *gem*-CH_3), 1.38 (3H, s, *gem*-CH_3), 2.56 (1H, dd, J = 15.6, 9.9, 4-C**H**), 2.84 (1H, d, J = 10.1, 2-C**H**), 3.22 (1H, dd, J = 15.6, 5.4, 4-C**H**), 3.37 (1H, td, J = 9.9, 5.4, 3-C**H**), 3.46 (3H, s, 3-OCH_3), 6.61 (1H, dd, J = 8.2, 2.5, 6-Ar**H**), 6.78 (1H, d, J = 2.5, 8-Ar**H**), 6.88 (1H, d, J = 8.2, 5-Ar**H**); δ_C (70 MHz, $CDCl_3$): 25.22, 27.49, 33.56, 40.00, 56.13, 60.25, 77.00, 112.79 (Ar-CH), 113.58 (Ar-CH), 122.82 (Ar-C), 129.61 (Ar-CH), 145.16 (Ar-C), 154.56 (Ar-C); FAB MS *m/z* 222 (MH^+, 100%); HRMS calc. for $C_{13}H_{20}NO_2$ 222.1494, found 222.1506; CHN calc. for $C_{13}H_{19}NO_2.HCl.1.5H_2O$: C 54.8, H 8.14, N 4.92, found: C 55.0, H 7.75, N 4.90

(3*R*)-7-Hydroxy-*N*-[(1*S*)-1-({[*trans*-7-hydroxy-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl]amino}methyl)-2-methylpropyl]-1,2,3,4-tetrahydro isoquinoline-3-carboxamide (66)

To a stirred solution of **82** (0.22 g, 0.38 mmol), Boc-D-Tic(OH)-OH (0.23 g, 0.42 mmol), 1-hydroxybenzotriazole hydrate (0.11 g, 0.42 mmol) and triethylamine (0.21 ml, 1.51 mmol) in 30:1 CH_2Cl_2: DMF (15 ml) at 0°C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17 g, 0.45 mmol) portionwise over 10 minutes. The reaction was stirred at 0°C for 1 hour then at RT for 15 hours. Water (10 ml) and $CHCl_3$ (15 ml) were added and the layers separated. The aqueous layer was extracted with $CHCl_3$ (2 × 20 ml), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography (1-3% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the amide as a

colourless foam (0.30 g). ^{1}H NMR showed the presence of a small amount of side product, therefore Boc-deprotection was carried out without further purification. The amide was redissolved in CH_2Cl_2 (20 ml) and trifluoroacetic acid (0.38 ml, 5.16 mmol) was added dropwise at RT. The reaction was stirred at RT for 18 hours, then quenched by the cautious addition of aq. sat. $NaHCO_3$ (15 ml). The aqueous layer was further basified (to pH 9) with conc. NH_4OH, then the layers were separated. The aqueous layer was extracted with 4:1 $CHCl_3$: EtOH (2 × 30 ml), and the combined organic layers were washed with brine (15 ml), dried ($MgSO_4$), filtered and evaporated to afford the title product as a colourless oil (0.25 g, 72% over two steps); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.13; δ_H (400 MHz, CD_3OD): 0.90 (3H, d, J = 7.2, Val-C**H**$_3$CHCH$_3$), 0.92 (3H, d, J = 6.4, Val-C**H**$_3$CHCH$_3$), 1.06 + 1.09 (3H, s, diast. *gem*-C**H**$_3$), 1.28 + 1.29 (3H, s, diast. *gem*-C**H**$_3$), 1.81 + 1.88 (1H, oct., J = 6.8, diast. Val-CH$_3$C**H**CH$_3$), 2.37 + 2.40 (1H, d, J = 9.6, diast. 2-C**H**), 2.56 (1H, m, Tic-CHC**H**$_2$Ar), 2.64-2.76 (2H, m, 4-C**H** + Val-NHC**H**$_2$CH), 3.00-3.11 (2H, m, Val-NHC**H**$_2$CH + Tic-CHC**H**$_2$Ar), 3.18 + 3.19 (1H, d-*pseudo*-t, J = 15.6, 6.0, 4-C**H**), 3.40 (4H, m, diast. 3-OC**H**$_3$ + 3-C**H**), 3.47 (1H, ddd, J = 10.8, 4.8, 1.6, Val-CH$_2$C**H**NH), 3.65-3.82 (1H, m, Tic-NHCOC**H**CH$_2$), 3.89 (2H, s, Tic-NHC**H**$_2$Ar), 6.48 (1H, d, J = 2.4, Tic-Ar**H**), 6.57 + 6.58 (1H, dd, J = 8.4, 2.4, diast. 6-Ar**H**), 6.62 (1H, dt, J = 8.4, 2.4, Tic-Ar**H**), 6.71 + 6.73 (1H, d, J = 2.4, diast. 8-Ar**H**), 6.82 + 6.84 (1H, d, J = 8.4, diast. 5-Ar**H**), 6.93 (1H, d, J = 8.4, Tic-Ar**H**); δ_C (100 MHz, $CDCl_3$): 18.12, 18.76, 19.15 + 19.34 (diast.), 26.13 + 26.19 (diast.), 27.99, 30.11 + 30.36 (diast.), 30.45 + 30.56 (diast.), 34.72 + 34.78 (diast.), 41.12 + 41.21 (diast.), 47.23 + 47.32 (diast.), 53.36 + 53.60 (diast.), 54.62 + 55.08 (diast.), 56.60 + 56.76 (diast.), 68.18 + 68.43 (diast.), 78.45 + 78.68 (diast.), 112.06 + 112.09 (diast. Ar-CH), 112.92 + 112.95 (diast. Ar-CH), 113.63 (Ar-CH), 113.93 (Ar-CH), 123.08 + 123.18 (diast. Ar-C), 124.75 + 124.80 (diast. Ar-C), 129.81 (Ar-CH), 129.93 + 129.97 (diast. Ar-CH), 136.42 + 136.50 (diast. Ar-C), 146.15 + 146.21 (diast. Ar-C), 154.98 + 155.06 (diast. Ar-C), 173.71 + 173.91 (diast. C=O); FAB MS: submitted; CHN: submitted

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphtho[2,3]azirene (67)

To a stirred solution of sodium bis(2-methoxyethoxy)aluminium hydride (14.1 ml, 3.5M solution in toluene, 49.3 mmol) in anhydrous THF (60 ml) at RT was added *N*-methylbutylamine (0.15 ml, 1.23 mmol). The flask was fitted with a pressure-equalising dropping funnel containing a solution of oxime **37** (2.70 g, 12.3 mmol) in anhydrous THF (30 ml) and the system purged with nitrogen. The oxime solution was subsequently added dropwise to the flask at RT over 30 minutes, after which the reaction was allowed to stir for 15 minutes until the evolution of hydrogen had ceased. The mixture was heated to reflux for 18 hours then allowed to return to RT. Sodium sulfate decahydrate was added (initially in small portions) until a granular precipitate of metal salts was obtained. The salts were separated by suction filtration and washed with THF (2 × 20 ml). The filtrate was then concentrated *in vacuo* to yield a brown oil. Column chromatography (1-2% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow oil (1.93 g, 74%); R_f (10% MeOH: 89% DCM: 1% NH_4OH) 0.51; ν_{max} (film) 3236 (O-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.23 (3H, s, *gem*-CH_3), 1.51 (3H, s, *gem*-CH_3), 2.12 (1H, d, J = 6.2, 2-CH), 2.47 (1H, d, J = 6.2, 3-CH), 3.14 (2H, s, 4-CH_2), 3.78 (3H, s, 7-OCH_3), 6.69 (1H, dd, J = 8.2, 2.5, 6-CH), 6.85 (1H, d, J = 2.5, 8-CH), 6.96 (1H, d, J = 8.2, 5-CH); δ_C (67.8 MHz; $CDCl_3$) 26.90, 29.36, 29.49, 29.54, 35.94, 41.31, 55.09, 111.38 (Ar-CH), 111.81 (Ar-CH), 122.58 (Ar-C), 130.43 (Ar-CH), 142.83 (Ar-C), 158.64 (Ar-C); EI MS *m/z* 203 (M^+, 60%)

1,1-Dimethyl-1,2,3,4-tetrahydronaphtho[2,3]aziren-7-ol (68)

To a stirred solution of methyl ether **67** (2.94 g, 14.5 mmol) in CH_2Cl_2 (70 ml) at -78°C under an atmosphere of nitrogen was added boron tribromide (28.9 ml, 1.0M solution in CH_2Cl_2, 28.9 mmol) dropwise *via* a syringe. When the addition was complete, the cooling bath was removed and the reaction was stirred for 18 hours. After this time the system was cooled to -78°C and quenched by the dropwise addition of a solution of triethylamine (10 ml) in MeOH (40 ml) *via* syringe, maintaining an atmosphere of nitrogen throughout. The system was allowed to return to RT and the solvent evaporated *in vacuo*. The resulting residue was partitioned between water (40 ml) and 3:1 $CHCl_3$: EtOH (80), and the layers were separated. The aqueous layer was extracted with 3:1 $CHCl_3$: EtOH (2 × 80 ml) and

the combined organic extracts were washed with water (70 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (2-5% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a brown foam (2.16 g, 79%); R_f (10% MeOH: 89% DCM: 1% NH_4OH) 0.39; ν_{max} (film) 3284 (br, O-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.21 (3H, s, *gem*-CH_3), 1.45 (3H, s, *gem*-CH_3), 2.16 (1H, d, J = 6.2, 2-CH), 2.51 (1H, d, J = 6.2, 3-CH), 3.07 (1H, dd, J = 15.3, 1.7, 4-CH), 3.15 (1H, dd, J = 15.3, 1.7, 4-CH), 6.55 (1H, dd, J = 8.2, 2.5, 6-CH), 6.71 (1H, d, J = 2.5, 8-CH), 6.82 (1H, d, J = 8.2, 5-CH); δ_C (70 MHz; $CDCl_3$): 27.18, 28.87, 29.59, 30.63, 35.84, 42.09, 113.14 (Ar-CH), 114.68 (Ar-CH), 119.93 (Ar-C), 130.90 (Ar-CH), 141.82 (Ar-C), 156.92 (Ar-C); EI MS *m/z* 189 (M^+, 20%)

tert-Butyl-7-[(_tert_-butoxycarbonyl)oxy]-1,1-dimethyl-1,2,3,4-tetrahydronaphtho [2,3]azirene-1-carboxylate (69)

To a stirred solution of **68** (0.70 g, 3.70 mmol), 4,4-dimethylaminopyridine (60 mg, 0.37 mmol) and triethylamine (1.04 ml, 7.40 mmol) in CH_2Cl_2 (20 ml) at RT was added di-*tert*-butyl dicarbonate (2.42 g, 11.1 mmol) in one portion. The reaction was stirred at RT for 5 hours, after which time water (15 ml) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml) and the combined organic layers were washed successively with aq. 1M HCl (40 ml) and aq. sat. $NaHCO_3$ (40 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (10% EtOAc: 90% Hexanes) afforded the title product as a colourless platelets (0.51 g, 65%); R_f (50% EtOAc: 50% Hexanes): 0.70; m.p. 183-184 °C; ν_{max} (film) 1757 (ester C=O), 1716 (carb. C=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.18 (3H, s, *gem*-CH_3), 1.38 (9H, s, NBoc-$(CH_3)_3$), 1.44 (3H, s, *gem*-CH_3), 1.52 (9H, s, OBoc-$(CH_3)_3$), 2.52 (1H, d, J = 6.7, 2-CH), 2.94 (1H, m, 3-CH), 3.02 (1H, dd, J = 15.6, 1.5, 4-CH), 3.27 (1H, d, J = 15.6, 2.2, 4-CH), 6.92 (1H, dd, J = 8.2, 2.5, 6-CH), 6.98 (1H, d, J = 8.2, 5-CH), 7.05 (1H, d, J = 2.5, 8-CH); δ_C (70 MHz, $CDCl_3$): 18.96, 22.84, 24.06, 24.22, 25.25, 25.58, 27.92, 31.88, 33.12, 43.81, 77.00 (Boc-C), 79.50 (Boc-C), 114.70 (Ar-CH), 115.54 (Ar-CH), 124.57 (Ar-C), 126.48 (A-CH), 139.61 (C=O), 146.42 (C=O); FAB MS *m/z* 390 (MH^+, 40%)

trans-2-[(_tert_-Butoxycarbonyl)amino]-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-yl-_tert_-butyl carbonate (70)

To a stirred solution of **69** (0.52 g, 1.34 mmol) in MeOH (10 ml) at RT was added pyridinium *p*-toluenesulfonate (0.17 g, 0.68 mmol). The mixture was stirred at RT for 15 h under an atmosphere of nitrogen, after which time the solvent was evaporated *in vacuo*. Water (10 ml) and CH_2Cl_2 (30 ml) were added to the residue and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic extracts were washed with water (50 ml) and brine (40 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (10% EtOAc: 90% Hexanes) afforded the title product as a light yellow oil (0.45 g, 80%); R_f (50% EtOAc: 50% Hexanes): 0.59; ν_{max} (film) 1757 (ester C=O), 1704 (carb. C=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.12 (3H, s, *gem*-CH_3), 1.32 (3H, s, *gem*-CH_3), 1.41 (9H, s, NBoc-$(CH_3)_3$), 1.50 (9H, s, OBoc-$(CH_3)_3$), 2.78 (1H, dd, *J* = 16.3, 8.9, 4-CH), 3.20 (1H, dd, *J* = 16.3, 5.4, 4-CH), 3.38 (3H, s, 3-OCH_3), 3.40-3.48 (1H, m, 3-CH), 3.79 (1H, t, *J* = 9.6, 2-CH), 4.46 (1H, d, *J* = 9.6, N-H), 6.92 (1H, dd, *J* = 8.2, 2.2, 6-CH), 6.99 (1H, d, *J* = 8.2, 5-CH), 7.04 (1H, d, *J* = 2.2, 8-CH); δ_C (70 MHz, $CDCl_3$): 15.19, 22.01, 28.70, 29.42, 35.39, 41.00, 57.44, 59.86, 77.00, 77.90 (Boc-C), 84.32 (Boc-C), 120.21 (Ar-CH), 120.38 (Ar-CH), 130.81 (Ar-C), 130.92 (Ar-CH), 146.39 (Ar-C), 150.76 (Ar-C), 152.95 (C=O), 157.64 (C=O); FAB MS *m/z* 422 (MH^+, 35%)

trans-3-Methoxy-1,1-dimethyl-2-{[(_E_)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydronaphthalen-7-ol (74)

The procedure used for the preparation of *ortho*-NO_2 compound **59** was employed. Aminotetralin **65** (69 mg, 0.31 mmol) was treated with *trans*-cinnamaldehyde (47 µl, 0.37 mmol) and sodium borohydride (47 mg, 1.23 mmol). Column chromatography (3% MeOH: 96% CH_2Cl_2: 1% NH_4OH) afforded the title product as a colourless oil (86 mg, 82%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.26; ν_{max} (film) 3327 (O-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.18 (3H, s, *gem*-CH_3), 1.38 (3H, s, *gem*-CH_3), 2.59 (1H, d, *J* = 9.9, 2-CH), 2.66 (1H, dd, *J* = 15.6, 9.6, 4-CH), 3.25 (1H, dd, *J* = 15.6, 5.4, 4-CH), 3.48 (3H, s, 3-OCH_3), 3.48-3.58 (2H, m, 3-CH + $NHCH_2CH$), 3.73 (2H, dd, *J* = 13.6, 6.2, $NHCH_2CH$), 6.33 (1H, dt, *J* = 15.8, 6.2, CH_2CH=CH), 6.54 (1H, d, *J* = 15.8, CH=CHPh), 6.61 (1H, dd, *J* =

8.2, 2.5, 6-ArH), 6.78 (1H, d, J = 2.5, 8-ArH), 6.90 (1H, d, J = 8.2, 5-ArH), 7.15-7.37 (5H, m, 5 × Ar-H); δ_C (70 MHz, $CDCl_3$): 24.82, 26.61, 33.28, 39.54, 52.43, 55.17, 65.43, 77.00, 111.70 (Ar-CH), 112.17 (Ar-CH), 122.78 (Ar-C), 124.67 (Ar-CH), 125.64 (Ar-CH), 126.89 (Ar-CH), 127.61 (Ar-CH), 128.39 (Ar-CH), 129.53 (Ar-CH), 135.88 (Ar-C), 145.02 (Ar-C), 152.98 (Ar-C); FAB MS *m/z* 338 (MH^+, 80%); HRMS calc. for $C_{22}H_{28}NO_2$ 338.2120, found 338.2119; CHN anal. calc. for $C_{22}H_{27}NO_2.HCl.0.5H_2O$: C 69.0, H 7.63, N 3.66, found: C 68.6, H 7.71, N 3.96

trans-2-[(Cyclopropylmethyl)amino]-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (75)

To a stirred solution of **65** (0.24 g, 1.08 mmol) in 4:1 1,2-dichloroethane: DMF (15 ml) at RT was added cyclopropanecarboxaldehyde (0.12 ml, 1.63 mmol). This was followed immediately by the addition of sodium triacetoxyborohydride (0.34 g, 1.63 mmol) in one portion. The reaction was stirred at RT under an atmosphere of nitrogen for 16 hours, after which it was quenched by the dropwise addition of aq. sat. $NaHCO_3$ (10 ml). After the effervescence had subsided, the two-phase system was separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were washed with water (30 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (2-4% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow oil which solidified on standing (70 mg, 23%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.30; m.p. 120-122 °C; ν_{max} (KBr) 3327 (O-H), 2819 ($COCH_3$) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.13 (2H, m, $CH(CH_2)_2$), 0.46 (2H, m, $CH(CH_2)_2$), 1.01 (1H, m, $CH(CH_2)_2$), 1.18 (3H, s, *gem*-CH_3), 1.38 (3H, s, *gem*-CH_3), 2.49 (1H, d, J = 9.6, 2-CH), 2.59-2.66 (2H, m, $CH_2CH(CH_2)_2$ + 4-CH), 2.71 (1H, dd, J = 11.6, 7.2, $CH_2CH(CH_2)_2$), 3.23 (1H, dd, J = 16.0, 5.6, 4-CH), 3.44 (3H, s, 3-OCH_3), 3.50 (1H, td, J = 9.6, 5.2, 3-CH), 3.96 (2H, br-s, NH + OH), 6.61 (1H, dd, J = 8.4, 2.6, 6-ArH), 6.77 (1H, d, J = 2.6, 8-ArH), 6.88 (1H, d, J = 8.4, 5-ArH); δ_C (100 MHz, $CDCl_3$): 0.00, 0.37, 8.40, 23.20, 24.99, 31.51, 53.41, 54.31, 64.68, 75.17, 110.04 (Ar-CH), 110.59 (Ar-CH), 120.63 (Ar-C), 126.72 (Ar-CH), 143.31 (Ar-C), 151.44 (Ar-C); FAB MS *m/z* 277 (MH^+, 100%); HRMS submitted; CHN calc. for $C_{17}H_{25}NO_2.HCl$: C 65.5, H 8.40, N 4.49, found: C 65.1, H 8.61, N 4.12

***trans*-2-(Allylamino)-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (76) and *trans*-2-(diallylamino)-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-7-ol (77)**

To a stirred solution of **65** (0.29 g, 1.31 mmol) and allyl bromide (0.16 ml, 2.10 mmol) in anhydrous THF (15 ml) at RT was added sodium carbonate (0.25 g, 3.28 mmol) and tetra-*n*-butylammonium iodide (97 mg, 0.26 mmol). The reaction was heated to reflux under an atmosphere of nitrogen for 24 hours, then allowed to cool to RT. The solvent was evaporated *in vacuo* and the residue partitioned between $CHCl_3$(20 ml) and water (15 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to yield a yellow oil. Column chromatography (0-5% MeOH: CH_2Cl_2: 1% NH_4OH) afforded firstly dialkylated product **57** as a yellow oil which solidified on standing (0.14 g, 35%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.68; m.p. 127-128 °C; ν_{max} (KBr) 3355 (O-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.14 (3H, s, *gem*-CH_3), 1.34 (3H, s, *gem*-CH_3), 2.63 (1H, dd, *J* = 15.2, 10.0, 4-C**H**), 2.79 (1H, d, *J* = 10.4, 2-C**H**), 3.27 (1H, dd, *J* = 15.2, 5.6, 4-C**H**), 3.31-3.38 (4H, m, 2 × CH_2CH=CH_2), 3.43 (3H, s, 3-OCH_3), 3.67 (1H, td, *J* = 10.4, 5.6, 3-C**H**), 5.03 (2H, d, *J* = 9.6, 2 × CH_2CH=CH_2), 5.16 (2H, br-d, *J* = 16.2, 2 × CH_2CH=CH_2), 5.86 (1H, ddt, *J* = 16.2, 10.4, 6.0, CH_2CH=CH_2), 6.59 (1H, dd, *J* = 8.2, 2.4, 6-Ar**H**), 6.76 (1H, d, *J* = 2.4, 8-Ar**H**), 6.89 (1H, d, *J* = 8.2, 5-Ar**H**); δ_C (100 MHz, $CDCl_3$): 27.22, 29.38, 30.96, 35.87, 42.20, 55.79, 67.43, 76.50, 113.32 (Ar-CH), 115.66 (broad: CH=CH_2 + Ar-CH), 124.58 (Ar-C), 129.83 (Ar-CH), 138.35 (CH=CH_2), 147.73 (Ar-C), 153.97 (Ar-C); FAB MS *m/z* 301 (M^+, 100%); HRMS submitted; CHN calc. for $C_{19}H_{27}NO_2$.HCl.0.25H_2O: C 66.7, H 8.39, N 4.09, found: C 66.8, H 8.24, N 4.11

Continued elution afforded monoalkylated product **56** as a yellow oil which solidified on standing (0.17 g, 50%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.36; m.p. 105-107 °C; ν_{max} (KBr) 3415 (O-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.16 (3H, s, *gem*-CH_3), 1.36 (3H, s, *gem*-CH_3), 2.54 (1H, d, *J* = 9.6, 2-C**H**), 2.64 (1H, dd, *J* = 15.6, 9.6, 4-C**H**), 3.23 (1H, dd, *J* = 16.0, 5.6, 4-C**H**), 3.34 (1H, dd, *J* = 14.0, 6.4, CH_2CH=CH_2), 3.45 (3H, s, 3-OCH_3), 3.48 (1H, td, *J* = 10.0, 5.6, 3-C**H**), 3.57 (1H, dd, *J* = 14.0, 6.4, CH_2CH=CH_2), 5.06 (1H, dd, *J* = 10.4, 1.4, CH_2CH=CH_2), 5.20

(1H, dd, J = 17.6, 1.4, $CH_2CH{=}CH_2$), 5.95 (1H, ddt, J = 17.4, 10.4, 6.0, $CH_2CH{=}CH_2$), 6.60 (1H, dd, J = 8.2, 2.8, 6-ArH), 6.77 (1H, d, J = 2.8, 8-ArH), 6.89 (1H, d, J = 8.2, 5-ArH); δ_C (100 MHz, $CDCl_3$): 26.36, 28.14, 34.78, 41.04, 54.56, 56.70, 66.94, 78.46, 113.20 (Ar-CH), 113.64 (Ar-CH), 115.79 ($CH{=}CH_2$), 124.17 (Ar-C), 129.96 (Ar-CH), 137.49 ($CH{=}CH_2$), 146.67 (Ar-C), 154.34 (Ar-C); FAB MS *m/z* 263 (MH^+, 100%); HRMS submitted; CHN calc. for $C_{16}H_{23}NO_2.HCl.0.25H_2O$: C 63.6, H 8.17, N 4.63, found: C 63.5, H 8.05, N 4.66

trans-3-Methoxy-1,1-Dimethyl-2-(propylamino)-1,2,3,4-tetrahydro naphthalen-7-ol (78)

To a stirred solution of **65** (0.19 g, 0.86 mmol) and 1-bromopropane (94 µl, 1.03 mmol) in anhydrous THF (10 ml) at RT was added sodium carbonate (0.23 g, 2.15 mmol) and tetra-*n*-butylammonium iodide (0.16 g, 0.26 mmol). The reaction was heated at reflux under an atmosphere of nitrogen for 44 hours, before the addition of further sodium carbonate (0.14 g, 0.86 mmol) and 1-bromopropane (78 µl, 0.86 mmol). Heating was continued for a further 24 hours, after which the reaction was allowed to return to RT. The solvent was removed *in vacuo* and the residue was partitioned between water (20 ml) and $CHCl_3$ (30 ml). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 × 30 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (2-3% MeOH: CH_2Cl_2: 1% NH_4OH) afforded a yellow oil (0.18 g) which was shown by NMR to be a mixture of the product and tetra-*n*-butylammonium iodide. The crude product was subsequently redissolved in EtOAc (50 ml) and washed with water (3 × 20 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the pure title product as a colourless oil which solidified on standing (93 mg, 43%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.21; m.p. 116-118 °C; ν_{max} (KBr) 3415 (O-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.92 (3H, t, J = 7.2, $CH_2CH_2CH_3$), 1.16 (3H, s, *gem*-CH_3) , 1.37 (3H, s, *gem*-CH_3), 1.53 (2H, sext. d, J = 7.6, 1.6, $CH_2CH_2CH_3$), 2.51 (1H, d, J = 10.0, 2-CH), 2.65 (2H, m, $CH_2CH_2CH_3$ + 4-CH), 2.89 (1H, ddd, J = 11.2, 8.0, 6.4, $CH_2CH_2CH_3$), 3.23 (1H, dd, J = 16.0, 5.6, 4-CH), 3.44 (3H, s, 3-OCH_3), 3.50 (1H, td, J = 9.6, 5.6, 3-CH), 4.11 (2H, br-s, NH + OH), 6.60 (1H, dd, J = 8.0, 2.4, 6-ArH), 6.77 (1H, d, J = 2.4, 8-ArH), 6.88 (1H, d, J = 8.0, 5-ArH); δ_C

(100 MHz, $CDCl_3$): 11.78, 23.53, 26.38, 28.27, 34.66, 41.00, 54.33, 56.58, 68.20, 78.14, 113.23 (Ar-CH), 113.80 (Ar-CH), 123.79 (Ar-C), 129.90 (Ar-CH), 146.49 (Ar-C), 154.66 (Ar-C); FAB MS *m/z* 265 (MH^+, 100%); HRMS submitted; CHN calc. for $C_{16}H_{25}NO_2.HCl.0.25H_2O$: C 63.1, H 8.78, N 4.60, found: C 63.2, H 8.85, N 4.27

trans-3-Methoxy-1,1-dimethyl-2-[(3-phenylpropyl)amino]-1,2,3,4-tetrahydro naphthalen-7-ol (79)

To a stirred solution of **65** (0.12 g, 0.54 mmol) and 1-bromo-3-phenylpropane (0.27 ml, 1.36 mmol) in anhydrous THF (7ml) was added sodium carbonate (0.23 g, 2.17 mmol) and tetra-*n*-butylammonium iodide (0.10 g, 0.27 mmol). The reaction was heated at reflux under an atmosphere of nitrogen for 60 hours then allowed to cool to RT. The solvent was evaporated *in vacuo* and the residue redissolved in EtOAc (40 ml). It was then subsequently washed with water (3 × 20 ml), brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (2% MeOH: 97% CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow oil (0.10 g, 54%); ν_{max} (film) 3328 (O-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.16 (3H, s, *gem*-CH_3), 1.36 (3H, s, *gem*-CH_3), 1.84 (2H, quint., J = 7.2, $CH_2CH_2CH_2$), 2.49 (1H, d, J = 10.0, 2-CH), 2.61-2.71 (3H, m, CH_2CH_2Ph + 4-CH), 2.74 (1H, dt, J = 11.4, 7.2, $CH_2CH_2CH_2$), 2.97 (1H, dt, J = 11.4, 7.2, $CH_2CH_2CH_2$), 3.22 (1H, dd, J = 16.0, 5.6, 4-CH), 3.45 (3H, s, 3-OCH_3), 3.47 (1H, td, J = 10.0, 5.6, 3-CH), 6.60 (1H, dd, J = 8.4, 2.6, 6-ArH), 6.77 (1H, d, J = 2.6, 8-ArH), 6.90 (1H, d, J = 8.4, 5-ArH), 7.15-7.20 (3H, m, 2 × Ar-H[*m*-CH_2CH_2] + Ar-H[*p*-CH_2CH_2]), 7.27 (2H, m, 2 × Ar-H[*o*-CH_2CH_2]); δ_C (100 MHz, $CDCl_3$): 26.38, 28.29, 32.39, 33.62, 34.72, 41.09, 51.79, 56.60, 68.01, 78.29, 113.20 (Ar-CH), 113.64 (Ar-CH), 124.13 (Ar-C), 125.63 (Ar-CH), 128.24 (Ar-CH), 128.37 (Ar-CH), 129.93 (Ar-CH), 142.73 (Ar-C), 146.73 (Ar-C), 154.37 (Ar-C); FAB MS *m/z* 340 (MH^+, 100%); HRMS submitted; CHN calc. for $C_{22}H_{29}NO_2.HCl.H_2O$: C 67.1, H 8.19, N 3.56, found: C 67.4, H 8.04, N 3.48

tert-Butyl-(1_S_)-1-({[_trans_-7-hydroxy-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-2-yl]amino}carbonyl)-2-methylpropylcarbamate (80)

To a stirred solution of **65** (0.45 g, 2.03 mmol) and Boc-L-valine (0.53 g, 2.44 mmol) in anhydrous THF (70 ml) at RT was added benzotriazol-1-

yloxytris(dimethylamino)-phosphonium hexafluorophosphate (1.08 g, 2.44 mmol) followed by triethylamine (1.43 ml, 10.2 mmol). The reaction was stirred at RT for 22 hours after which the solvent was evaporated *in vacuo*. The residue was partitioned between CH_2Cl_2 (40 ml) and water (30 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Column chromatography (20% EtOAc: 80% Hexanes) afforded the title product (1:1 mixture of diastereomers) as a colourless foam (0.46 g, 54%); R_f (50% EtOAc: 50% Hexanes): 0.43; ν_{max} (film) 3318 (O-H), 1694 (amide C=O), 1531 (amide N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.96 (3H, d, *J* = 6.8, Val-CH_3CHCH_3), 1.00 (3H, d, *J* = 6.4, Val-CH_3CHCH_3), 1.14 (3H, s, *gem*-CH_3), 1.26 + 1.29 (3H, s, diast. *gem*-CH_3), 1.44 + 1.46 (9H, s, diast. Boc-(CH_3)$_3$), 2.72 (1H, m, 4-CH), 3.19 (1H, *pseudo*-quint., *J* = 10.0, 4-CH), 3.33 + 3.37 (3H, s, diast. 3-OCH_3), 3.50 (1H, *pseudo*-q, *J* = 10.0, 3-CH), 3.88 (1H, *pseudo*-t, *J* = 8.2, Val-CH_3CHCH_3), 4.20 (1H, *pseudo*-t, *J* = 10.0, 2-CH), 5.35 + 5.40 (1H, d, *J* = 8.8, Val-COCHNHBoc), 6.28 + 6.46 (1H, d, *J* = 8.8, diast. CHNHCO), 6.68 (1H, d-*pseudo*-t, *J* = 8.4, 2.0, diast. 5-ArH), 6.81 (1H, *pseudo*-t, *J* = 2.4, diast. 8-ArH), 6.87 (1H, d, *J* = 8.6, 6-ArH); δ_C (100 MHz, $CDCl_3$): 17.97 + 18.24 (diast.) , 19.18 + 19.53 (diast.), 26.77 + 26.87 (diast.), 27.91 + 28.10 (diast.), 28.32, 30.28 + 30.42 (diast.), 34.23, 40.06, 56.12, 57.70, 60.93 + 61.15 (diast.), 75.30 + 75.43 (diast.), 79.98 + 80.21 (diast.), 113.11 + 113.16 (diast. Ar-CH), 114.28 + 114.32 (diast. Ar-CH), 122.99 + 123.07 (diast. Ar-C), 130.04 (Ar-CH), 144.84 + 144.94 (diast. Ar-C), 155.20 (C=O), 156.21 + 156.29 (diast. Ar-C), 172.73 + 172.84 (diast. C=O); FAB MS *m/z* 421 (MH^+, 100%); HRMS calc. for $C_{23}H_{37}N_2O_5$ 421.2702, found 421.2708

(2*S*)-2-Amino-*N*-[*trans*-7-hydroxy-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-2-yl]-3-methylbutanamide (81)

To a stirred solution of **60** (0.46 g, 1.09 mmol) in CH_2Cl_2 (12 ml) at RT was added trifluoroacetic acid (0.81 ml, 10.9 mmol) dropwise. The reaction was stirred at RT for 3 hours then quenched by the dropwise addition of aq. sat. $NaHCO_3$ (10 ml). The pH was adjusted to 9 with conc. NH_4OH and CH_2Cl_2 (15 ml) was added. The two-phase system was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and

concentrated *in vacuo*. Column chromatography (6% MeOH: 93% CH_2Cl_2: 1% NH_4OH) afforded the title product as a colourless foam (0.23 g, 66%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.19; ν_{max} (film) 3307 (O-H), 1652 (amide C=O), 1531 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.90 (3H, d, *J* = 6.8, Val-CH_3CHCH_3), 1.03 (3H, d, *J* = 6.8, Val-CH_3CHCH_3), 1.16 + 1.17 (3H, s, diast. *gem*-CH_3), 1.27 (3H, s, *gem*-CH_3), 2.36 (1H, d septet, *J* = 6.8, 3.6, Val-CH_3CHCH_3), 2.74 (1H, dd, *J* = 15.6, 9.2, 4-CH), 3.20 (1H, *pseudo*-dt, *J* = 15.6, 5.2, diast. 4-CH), 3.35 (1H, m, $NHCOCHNH_2$), 3.38 + 3.40 (3H, s, diast. 3-OCH_3), 3.50 + 3.54 (1H, td, *J* = 9.6, 5.6, diast. 3-CH), 4.18 + 4.19 (1H, *pseudo*-t, *J* = 10.0, diast. 2-CH), 6.70 (1H, dd, *J* = 8.4, 2.4, 6-ArH), 6.82 (1H, *pseudo*-t, *J* = 2.4, 8-ArH), 6.87 (1H, d, *J* = 8.4, 5-ArH), 7.39 + 7.54 (1H, d, *J* = 10.4, diast. CHNHCO); δ_C (100 MHz, $CDCl_3$): 15.71 + 16.35 (diast.), 19.83 + 19.90 (diast.), 26.88 + 26.93 (diast.), 28.15 + 28.30 (diast.), 30.82 + 30.92 (diast.), 31.01, 34.20, 40.08, 56.06 + 56.17 (diast.), 57.29 + 57.49 (diast.), 60.24 + 60.54 (diast.), 75.59 + 75.73 (diast.), 113.35 (Ar-CH), 114.42 (Ar-CH), 122.86 + 122.89 (diast. Ar-C), 129.98 (Ar-CH), 144.83 + 144.85 (diast. Ar-C), 155.46 (Ar-C), 175.29 + 175.48 (diast. C=O); FAB MS *m/z* 321 (MH^+, 100%); HRMS calc. for $C_{18}H_{29}N_2O_3$ 321.2178, found 321.2174

trans-2-{[(2*S*)-2-Amino-3-methylbutyl]amino}-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (82) _via_ reduction of amide 61

To a stirred solution of **61** (0.16 g, 0.49 mmol) in anhydrous THF (10 ml) at 0°C under an atmosphere of nitrogen was added borane.DMS complex (2.0M solution in THF, 2.47 ml, 4.93 mmol) dropwise over 10 minutes. The reaction was allowed to warm to RT and stirred for 1 hour, after which it was heated to reflux for a further 19 hours. The mixture was then cooled to –20°C and quenched by the dropwise addition of MeOH (0.5 ml), cautiously at first as vigorous effervescence occurred. After stirring at RT for 1 hour, a 1M solution of HCl in propan-2-ol (0.2 ml) was added and stirring was continued for a further 30 minutes. The solvent was then evaporated *in vacuo* and the residue adjusted to pH 9 by the addition of aq. sat. $NaHCO_3$. 4:1 $CHCl_3$: EtOH (15 ml) was added and the layers separated. The aqueous layer was extracted with 4:1 $CHCl_3$: EtOH (4 × 15 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH) afforded the title product

as a colourless oil (0.13 g, 87%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.15; ν_{max} (film) 1610 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.97 (6H, *pseudo*-t, J = 6.8, diast. Val-C**H**$_3$CHCH$_3$), 1.16 (3H, s, *gem*-C**H**$_3$), 1.36 (3H, s, *gem*-C**H**$_3$), 1.71 (1H, oct., J = 6.8, Val-CH$_3$C**H**CH$_3$), 2.46 + 2.47 (1H, d, J = 9.6, diast. 2-C**H**), 2.65 (2H, dd + m, J = 16.4, 9.6, 4-C**H** + Val-C**H**$_2$CHNH$_2$), 2.80 + 2.93 (1H, d, J = 12.4, diast. Val-C**H**$_2$CHNH$_2$), 3.19-3.30 (2H, m, 4-C**H** + Val-CH$_2$C**H**NH$_2$), 3.43-3.51 (4H, m, diast. 3-OC**H**$_3$ + 3-C**H**), 3.96 (4H, br-s, O**H** + N**H** + N**H**$_2$), 6.66 (1H, d-*pseudo*-t, J = 8.4, 2.4, diast. 6-Ar**H**), 6.80 (1H, d, J = 2.4, 8-Ar**H**), 6.89 (1H, 2 × d, J = 8.4, diast. 5-Ar**H**); δ_C (100 MHz, $CDCl_3$): 18.51 + 18.64 (diast.), 19.24 + 19.34 (diast.), 26.49 + 26.52 (diast.), 28.20 + 28.25 (diast.), 31.54 + 31.61 (diast.), 34.89, 41.04 + 41.49 (diast.), 54.79 + 55.84 (diast.), 56.54 + 56.67 (diast.), 57.29 + 57.33 (diast.), 67.89 + 68.07 (diast.), 78.48 + 79.06 (diast.), 113.54 + 113.67 (diast. Ar-CH), 114.13 + 114.19 (diast. Ar-CH), 122.93 + 123.08 (diast. Ar-C), 129.78 + 129.85 (diast. Ar-CH), 146.34 (Ar-C), 155.61 + 155.64 (diast. Ar-C); FAB MS *m/z* 307 (MH^+, 100%); HRMS calc. for $C_{18}H_{31}N_2O_2$ 307.2386, found 307.2386

trans-2-{[(2*S*)-2-Amino-3-methylbutyl]amino}-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (82) _via_ Boc-deprotection of 91

To a stirred solution of **91** (0.35 g, 0.86 mmol) in CH_2Cl_2 (15 ml) at RT was added trifluoroacetic acid (0.64 ml, 8.61 mmol) dropwise. The reaction was stirred at RT for 24 hours after which time it was neutralised by the cautious addition of sat. aq. $NaHCO_3$. The pH was adjusted to 9 with conc. NH_4OH and the two-phase system was separated. The aqueous layer was extracted with 4:1 $CHCl_3$: EtOH (3 × 20 ml) and the combined organic layers were washed with brine (20 ml) then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (1-5% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a colourless oil (0.22 g, 83%). See above procedure for data.

tert-Butyl-(3*R*)-7-hydroxy-3-({[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}carbonyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (87)

To a stirred solution of L-Valinol (0.16 g, 1.54 mmol), Boc-D-Tic(OH)-OH (0.41 g, 1.40 mmol) and triethylamine (0.58 ml, 4.19 mmol) in CH_2Cl_2 (30 ml) at RT was added benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate

(0.80 g, 1.54 mmol). The reaction was allowed to stir at RT for 16 hours after which time water (15 ml) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with 1M HCl (30 ml), aq. sat. $NaHCO_3$ (30 ml) then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (4% MeOH: 95.5% CH_2Cl_2: 0.5% NH_4OH) afforded the title product (0.51 g, 96%). Characterisation was not carried out due to poor solubility (see Section 3.3.3).

tert-Butyl-(1*S*)-1-({[*trans*-7-hydroxy-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydro naphthalen-2-yl]amino}methyl)-2-methylpropylcarbamate (91)

To a stirred solution of Boc-L-valinol (0.29 g, 1.43 mmol) in CH_2Cl_2 (5 ml) at RT was added a solution of Dess-Martin periodinane (0.91 g, 2.14 mmol) in CH_2Cl_2 (5 ml) dropwise. The reaction was stirred at RT for 1.5 hours then diluted with diethyl ether (10 ml). Sat. aq. $NaHCO_3$ (20 ml) was added to quench the reaction and the mixture was stirred for a further 15 minutes. The resulting two-phase system was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with brine (10 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude aldehyde as a colourless oil (0.27 g); R_f (50% EtOAc: 50% Hexanes): 0.53. This was then redissolved in 4:1 1,2-dichloroethane: DMF (20 ml) and aminotetralin **65** (0.25 g, 1.18 mmol) was added with vigorous stirring. When a clear solution had been obtained, sodium triacetoxyborohydride (0.45 g, 2.14 mmol) was added portionwise over 10 minutes at RT. The reaction was stirred under an atmosphere of nitrogen for 48 hours before cautiously quenching with aq. sat. $NaHCO_3$ (10 ml). When the effervescence had subsided, the layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Column chromatography (1-3% MeOH: CH_2Cl_2: 1% NH_4OH) afforded the title product as a colourless oil (0.37 g, 81%); ν_{max} (film) 3338 (O-H), 1684 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.90 (6H, *pseudo*-t, *J* = 6.8, Val-CH_3CHCH_3), 1.09 + 1.10 (3H, s, diast. *gem*-CH_3), 1.32 (3H, s, *gem*-CH_3), 1.45 (9H, s, Boc-$(CH_3)_3$), 1.78 (1H, m, Val-CH_3CHCH_3), 2.40 (1H, *pseudo*-t, *J* = 9.6, diast. 2-C**H**), 2.60 (1H, dd, *J* = 16.0, 10.4, 4-C**H**), 2.72 (1H, dd, *J* = 12.0, 3.6, Val-NHC**H**$_2$CH), 2.97 (1H, dd, *J* = 12.0, 6.8, Val-NHC**H**$_2$CH), 3.22 (1H, dd, *J* = 15.6,

5.6, 4-CH), 3.38-3.50 (2H, m, 3-CH + Val-NHCH$_2$CH), 3.43 + 3.44 (3H, s, diast. 3-OCH$_3$), 6.63 (1H, dd, *J* = 8.4, 2.4, 6-ArH), 6.80 (1H, *pseudo*-t, *J* = 2.4, diast. 8-ArH), 6.85 (1H, d, *J* = 8.4, 5-ArH); δ_C (100 MHz, $CDCl_3$): 18.52, 19.01, 26.22 + 26.29 (diast.), 27.89 + 27.95 (diast.), 28.37, 30.45, 34.86, 41.20, 53.35, 56.17, 56.46 + 56.55 (diast.), 67.97, 78.76 + 78.87 (diast.), 79.05, 113.17 + 113.20 (diast. Ar-CH), 113.70 (Ar-CH), 123.20 + 123.37 (diast. Ar-C), 129.73 (Ar-CH), 146.29 + 146.41 (diast. Ar-C), 154.94 (C=O), 156.48 + 156.72 (diast. Ar-C); FAB MS *m/z* 407 (MH^+, 100%); HRMS submitted

trans-1,1-Dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]amino}-3-pyrrolidin-1-yl-1,2,3,4-tetrahydronaphthalen-7-ol (92)

The procedure used for the preparation of **68** was followed, although an additional equivalent of boron tribromide was employed. Thus a solution of methyl ether **129** (0.13 g, 0.33 mmol) in CH_2Cl_2 (8 ml) was treated with boron tribromide (1.0 ml, 1.0M solution in CH_2Cl_2, 0.99 mmol) at -78°C and worked up as described for **68**. Column chromatography (2% MeOH: 97% CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow oil which solidified on standing (0.06 g, 49%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.24; m.p. 126-128 °C; ν_{max} (film) 3415 (O-H) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.21 (3H, s, *gem*-CH_3), 1.42 (3H, s, *gem*-CH_3), 1.75 (4H, m, py-N(CH_2)$_2$(CH_2)$_2$), 2.53 (2H, d, *J* = 10.6, 2-CH), 2.65 (4H, m, py-N(CH_2)$_2$(CH_2)$_2$), 2.83 (2H, m, 4-CH_2), 3.06 (1H, td, *J* = 9.9, 6.4, 3-CH), 3.43 (1H, ddd, *J* = 13.6, 6.9, 1.0, CH_2CH=CH), 3.63 (1H, dd, *J* = 13.6, 5.5, CH_2CH=CH), 4.09 (2H, br-s, OH + NH), 6.31 (1H, ddd, *J* = 15.8, 6.7, 5.7, CH_2CH=CH), 6.52 (1H, d, *J* = 15.8, CH=CHPh), 6.60 (1H, dd, *J* = 8.2, 2.5, 6-ArH), 6.80 (1H, d, *J* = 2.5, 8-ArH), 6.90 (1H, d, *J* = 8.2, 5-ArH), 7.15-7.35 (5H, m, CH=CHPh); δ_C (68 MHz, $CDCl_3$): 23.89, 26.17, 26.64, 28.98, 41.60, 47.62, 55.07, 55.72, 66.94, 113.10 (Ar-CH), 113.52 (Ar-CH), 126.06 (Ar-C), 126.35 (Ar-CH), 127.30 (Ar-CH), 128.58 (Ar-CH), 129.19 (Ar-CH), 130.07 (Ar-CH), 130.91 (Ar-CH), 137.39 (Ar-C), 147.30 (Ar-C), 154.26 (Ar-C); FAB MS submitted; CHN submitted

Attempted preparation of *trans*-2-amino-1,1-dimethyl-3-pyrrolidin-1-yl-1,2,3,4-tetrahydronaphthalen-7-ol dihydrobromide (96)

To a stirred solution of **98** (0.25 g, 0.47 mmol) in glacial acetic acid (7.5 ml) at RT was added aq. 48% hydrobromic acid (7.5 ml). The reaction was stirred at RT for 19 hours, then the solvent was evaporated *in vacuo* to leave the crude HBr salt as a crystalline solid. Recrystallisation from propan-1-ol/diethyl ether afforded 0.12g of colourless prisms.

Benzyl-7-{[(benzyloxy)carbonyl]oxy}-1,1-dimethyl-1,2,3,4-tetrahydronaphtho [2,3]azirene-1-carboxylate (97)

To a stirred solution of aziridine **68** (0.35 g, 1.85 mmol), triethylamine (1.04 ml, 7.40 mmol) and 4,4-dimethylaminopyridine (68 mg, 0.55 mmol) in CH_2Cl_2 (20 ml) at 0°C was added benzyl chloroformate (1.05 ml, 7.40 mmol) dropwise. The reaction was subsequently allowed to warm to RT and stirred for 16 hours. Aq. 2M HCl (15 ml) was then added and the two-phase system separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml), and the combined organic layers were washed with aq. sat. $NaHCO_3$ (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Column chromatography (20% EtOAc: 80% Hexanes) afforded the title product as a colourless oil (0.71 g, 84%); R_f (50% EtOAc: 50% Hexanes): 0.43; ν_{max} (film) 1761 and 1719 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.25 (3H, s, *gem*-CH_3), 1.62 (3H, s, *gem*-CH_3), 2.70 (1H, d, J = 6.4, 2-CH), 3.11 (2H, m, 3-CH + 4-CH), 3.37 (1H, dd, J = 17.6, 2.0, 4-CH), 5.12 (2H, s, NCO_2CH_2Ph), 5.29 (2H, s, OCO_2CH_2Ph), 7.01 (1H, dd, J = 8.4, 2.4, 6-ArH), 7.08 (1H, d, J = 8.4, 5-ArH), 7.14 (1H, d, J = 2.4, 8-ArH), 7.33-7.50 (10H, m, 10 × Cbz-ArH); δ_C (100 MHz, $CDCl_3$): 26.64, 28.72, 29.25, 35.68, 37.19, 47.55, 68.03, 70.30, 118.22 (Ar-CH) , 119.09 (Ar-CH), 128.03 (Ar-CH), 128.22 (Ar-CH), 128.48 (Ar-C), 128.54 (Ar-CH), 128.60 (Ar-CH), 128.72 (Ar-CH), 128.78 (Ar-CH), 130.34 (Ar-CH), 134.81 (Ar-C), 135.91 (Ar-C), 143.36 (Ar-C), 150.21 (Ar-C), 153.69 (C=O), 163.33 (C=O); FAB MS *m/z* 458 (MH^+, 95%); HRMS calc. for $C_{28}H_{28}NO_5$ 458.1967, found 458.1967

Benzyl-*trans*-2-{[(benzyloxy)carbonyl]amino}-1,1-dimethyl-3-pyrrolidin-1-yl-1,2,3,4-tetrahydronaphthalen-7-yl carbonate (98)

To a stirred solution of protected aziridine **97** (0.71 g, 1.55 mmol) in anhydrous THF (20 ml) at RT was added ytterbium (III) trifluoromethanesulfonate (96 mg, 0.15 mmol). The mixture was stirred at RT for 15 minutes before the dropwise addition of pyrrolidine (0.64 ml, 7.76 mmol). Stirring was continued for 18 hours at RT and then the solvent was evaporated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 ml) and water (15 ml), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml) and the combined organic layers were washed with water (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Column chromatography (30% EtOAc: 70% Hexanes) afforded the title product as a colourless oil (0.73 g, 89%); R_f (50% EtOAc: 50% Hexanes): 0.40; ν_{max} (film) 1703 and 1675 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.23 (3H, s, *gem*-**CH₃**), 1.61 (3H, s, *gem*-**CH₃**), 1.90 (4H, m, Py-N$(CH_2)_2$(**CH₂**)₂), 2.68 (1H, d, *J* = 6.4, 2-**CH**), 3.03-3.10 (2H, m, 3-**CH** + 4-**CH**), 3.30 (1H, dd, *J* = 17.2, 2.8, 4-**CH**), 3.39-3.49 (4H, m, Py-N(**CH₂**)₂$(CH_2)_2$), 5.11 (2H, s, NCO_2**CH₂**Ph), 5.18 (2H, s, OCO_2**CH₂**Ph), 6.66 (1H, dd, *J* = 8.4, 2.4, 6-Ar**H**), 6.84 (1H, d, *J* = 2.4, 8-Ar**H**), 6.92 (1H, d, *J* = 8.4, 5-Ar**H**), 7.32-7.43 (10H, m, 10 × Cbz-Ar**H**); δ_C (100 MHz, $CDCl_3$): 25.00 + 25.76 (2 × Py-CH_2), 26.64, 26.69, 28.93, 35.52, 37.51, 45.87 + 46.30 (2 × Py-CH_2), 47.77, 66.72, 67.96, 112.50 (Ar-CH), 113.72 (Ar-CH), 122.30 (Ar-CH), 127.90 (Ar-CH), 127.93 (Ar-CH), 128.04 (Ar-CH), 128.19 (Ar-CH), 128.48 (Ar-CH), 128.52 (Ar-CH), 130.44 (Ar-CH), 135.95 (Ar-C), 137.06 (Ar-C), 143.17 (Ar-C), 155.02 (Ar-C), 163.58 (Ar-C); FAB MS *m/z* 529 (MH^+, 45%); HRMS calc. for $C_{32}H_{37}N_2O_5$ 529.2702, found 529.2684

7-Azabicyclo[4.1.0]heptane (101)

To a stirred solution of sodium azide (8.03 g, 124 mmol) in 1:1 acetone: water (70 ml) at RT was added cyclohexene oxide (5.00 ml, 49.4 mmol) dropwise. The reaction was heated at reflux for 16 hours then allowed to cool to RT. The acetone was removed *in vacuo* and the resulting emulsion extracted with diethyl ether (3 × 40 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The crude azido-alcohol was subsequently redissolved in THF (60 ml) and triphenylphosphine (13.0 g, 49.4 mmol) was added in one portion. The mixture was heated to reflux for a further 16 hours before again allowing to cool to RT. The solvent was evaporated and *n*-

pentane (40 ml) added to the residue. Precipitated triphenylphosphine oxide was collected by suction filtration and washed with *n*-pentane (2 × 30 ml). The filtrate was concentrated *in vacuo* and the residue distilled under reduced pressure using a Kugel-Rohr oven (bpt. 95-100°C at 150 mmHg) to afford the title product as a colourless liquid (1.66 g, 35%); δ_H (270 MHz, $CDCl_3$): 1.18-1.35 (4H, m, ring), 1.79 (4H, s, ring), 2.19 (2H, s, ring), 3.22 (1H, d, J = 2.1, ring); δ_C (70 MHz, $CDCl_3$): 20.40, 24.82, 29.53

7-(3-Phenylpropyl)-7-azabicyclo[4.1.0]heptane (102)

To a vigorously stirred solution of **101** (0.57 g, 5.83 mmol) and 18-crown-6 (0.15 g, 0.58 mmol) in acetonitrile (20 ml) at RT was added potassium carbonate (3.22 g, 23.3 mmol). 1-Bromo-3-phenylpropane (0.89 ml, 5.83 mmol) was then added dropwise, followed immediately by lithium iodide (78 mg, 0.58 mmol). The reaction was heated at reflux for 40 hours then allowed to cool to RT. The solvent was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 (30 ml) and water (20 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with water (40 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Column chromatography (100% Hexanes to elute residual starting material, then 20% EtOAc: 80% Hexanes) afforded the title product as a yellow oil (0.56 g, 38%); δ_H (270 MHz, $CDCl_3$): 1.06-1.37 (4H, m, cyclohexyl), 1.38-1.43 (2H, m, cyclohexyl), 1.68-1.80 (4H, m, cyclohexyl), 1.86 (2H, quint, J = 7.4, CH_2CHPh), 2.23 (2H, t, J = 7.7, $NCH_2(CH_2)_2Ph$), 2.64 (2H, t, J = 7.7, $(CH_2)_2CH_2Ph$), 7.14-7.27 (5H, m, 5 × Ar-H)

***N*-[*trans*-2-Anilinocyclohexyl]-*N*-(3-phenylpropyl)amine (103)**

To a vigorously stirred solution of **102** (0.14 g, 0.65 mmol) in non-anhydrous acetonitrile (3 ml) at RT was added tris(pentafluorophenyl)borane (32 mg, 0.07 mmol), followed immediately by aniline (70 µl, 0.78 mmol). The reaction was heated at 70°C for 40 hours then allowed to cool to RT. The solvent was removed *in vacuo* and the residue redissolved in $CHCl_3$ (4 ml). Amberlyst A-21 ion-exchange resin (0.6 g) was added and the mixture stirred at RT for 3 hours. The resin was separated by suction filtration and washed with $CHCl_3$ (2 × 5 ml). The filtrate was concentrated *in vacuo* to yield an orange oil which was subsequently purified by

column chromatography (100% $CHCl_3$ to elute residual aniline, then 10% MeOH: 89% $CHCl_3$: 1% NH_4OH to elute product) to afford the title product as a light brown oil (0.21 g, 100%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.60; ν_{max} (film) 3344 and 1602 (N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.08-1.22 (2H, cyclo CH_2), 1.22-1.46 (2H, cyclo CH_2), 1.76-1.92 (4H, m, cyclo CH_2 + CH_2CH_2Ph), 2.15-2.28 (2H, cyclo CH_2), 2.37 (2H, td, J = 9.4, 3.6, $NHCH_2(CH_2)_2Ph$), 2.58 (1H, ddd, J = 11.2, 7.6, 6.8, $CHNH(CH_2)_3Ph$), 2.72 (2H, t, J = 7.6, $(CH_2)_2CH_2Ph$), 2.83 (1H, ddd, J = 11.2, 7.6, 6.4, CHNHPh), 6.74-6.82 (3H, m, 3 × Ar-H[*o* + *p*-NH]), 7.22-7.37 (7H, m, 7 × Ar-H); δ_C (100 MHz, $CDCl_3$): 24.77, 25.16, 31.43, 31.88, 32.70, 33.66, 46.33, 57.44, 62.33, 114.18 (Ar-CH), 117.83 (Ar-CH), 125.85 (Ar-CH), 128.40 (Ar-CH), 128.49 (Ar-CH), 129.39 (Ar-CH), 142.10 (Ar-C), 148.26 (Ar-C); FAB MS *m/z* 309 (MH^+, 100%); HRMS calc. for $C_{21}H_{29}N_2$ 309.2331, found 309.2326; CHN calc. for $C_{21}H_{28}N_2.2HCl.0.75H_2O$: C 63.9, H 8.04, N 7.09, found: C 63.9, H 7.79, N 6.74

_N_-Benzyl-_N_-methyl-_N_-{*trans*-2-[(3-phenylpropyl)amino]cyclohexyl}amine (104)

The procedure used for the preparation of **103** was followed, although different proportions of reagents were employed. Thus aziridine **102** was treated with *N*-benzylmethylamine (0.61 ml, 4.74 mmol) and tris(pentafluorophenyl)borane (0.12 g, 0.24 mmol) in acetonitrile (5 ml). After stirring at 70°C for 40 hours, the crude product was isolated according as described for **103**. Column chromatography (0-2% MeOH: $CHCl_3$) afforded the title product (0.25 g, 63%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.69; δ_H (270 MHz, $CDCl_3$): 1.06-1.33 (4H, m, cyclohexyl), 1.70 (1H, m, cyclohexyl), 1.79-1.93 (4H, m, CH_2CH_2Ph + cyclohexyl), 2.04-2.11 (1H, m, cyclohexyl), 2.12 (3H, s, NCH_3), 2.36-2.52 (3H, m, $NHCH_2CH_2$ + cyclohexyl CH), 2.66 (2H, t, J = 7.2, CH_2CH_2Ph), 2.75 (1H, td, J = 11.6, 6.7, cyclohexyl CH), 3.48 (1H, d, J = 13.3, NCH_2Ph), 3.64 (1H, d, J = 13.1, NCH_2Ph), 3.96 (1H, br s, N-H), 7.14-7.32 (10H, m, 10 × Ar-H; FAB MS *m/z* 337 (MH^+, 100%); HRMS calc. for $C_{23}H_{32}N_2$ 337.2644, found 337.2643

_N_-Benzyl-_N_-(cyclopropylmethyl)amine (109)

To a stirred solution of (aminomethyl)cyclopropane (0.60 ml, 7.00 mmol) in MeOH (4 ml) was added benzaldehyde (0.59 ml, 5.84 mmol) dropwise. The reaction was heated to reflux under an atmosphere of nitrogen for 2 hours before cooling to

0°C. Sodium borohydride (0.88 g, 23.3 mmol) was added portionwise over 2 hours to the imine whilst maintaining the temperature at 0°C. The cloudy mixture was allowed to warm to RT and stirred for 40 hours, then cooled back to 0°C. The reaction was then quenched by the dropwise addition of aq. 1M HCl (10 ml). The mixture was stirred at RT for 1 hour and the pH subsequently adjusted to 9 by the cautious addition of conc. NH_4OH. The two-phase system was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (1% MeOH: 98% $CHCl_3$: 1% NH_4OH) afforded the title product as a colourless liquid (0.99 g, 88%); δ_H (270 MHz, $CDCl_3$): 0.07 (2H, *pseudo*-q, J = 7.3, $CH(CH_2)_2$), ddd, J = 7.9, 5.7, 4.5, $CH(CH_2)_2$), 0.90-1.04 (1H, m, $CH(CH_2)_2$), 1.56 (1H, br-s, N-H), 2.47 (2H, d, J = 6.9, $NHCH_2CH$), 3.79 (2H, s, $NHCH_2Ph$), 7.24 (1H, m, Ar-H[*p*-CH_2NH]), 7.28-7.32 (4H, m, 4 × ArH)

[*N*-(4-Nitrophenylsulfonyl)imino]phenyliodinane (110)[130]

To a stirred mixture of 4-nitrobenzenesulfonamide (1.52 g, 7.52 mmol) and potassium hydroxide (1.05 g, 18.7 mmol) in MeOH (30 ml) at 0°C was added iodobenzene diacetate (2.42 g, 18.7 mmol). The reaction was allowed to warm to RT and stirred for 3 hours, during which time a cream precipitate formed. The precipitate was collected by suction filtration, washed with water (2 × 10 ml) and dried overnight in a desiccator to afford the title product as a cream solid (1.82 g, 60%); δ_H (270 MHz, DMSO-d_6): 7.45 (2H, m), 7.56 (1H, m), 7.95 (4H, m), 8.22 (2H, d, J = 8.9); δ_C (68 MHz, DMSO-d_6): 124.12, 125.02, 127.79, 128.28, 130.55, 131.26, 133.70, 137.67

7-[(4-Nitrophenyl)sulfonyl]-7-azabicyclo[4.1.0]heptane (111)

To a stirred solution of cyclohexene (0.30 ml, 2.96 mmol) in anhydrous acetonitrile (10 ml) at RT were added 4Å molecular sieves (0.6 g) followed by copper (II) trifluoromethanesulfonate (0.16 g, 0.44 mmol). To the resulting light blue solution was added nitrene donor species **110** (1.83 g, 4.44 mmol) in small portions over 4 hours. The reaction was stirred at RT for 18 hours and then the solvent was evaporated *in vacuo*. Column chromatography (10% EtOAc: 90% Hexanes) afforded the title product as a white solid (0.84 g, 77%); ν_{max} (KBr) 1541

(N=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.10-1.42 (4H, m, $(\mathbf{CH_2})_2(CH_2)_2(CH)_2N$), 1.67-1.82 (4H, m, $(CH_2)_2(\mathbf{CH_2})_2(CH)_2N$), 3.06 (2H, m, $(CH_2)_4(\mathbf{CH})_2N$), 8.08 (2H, d-*pseudo*-t, J = 8.9, 2.2, 2 × Ar-**H**[*o*-SO_2]), 8.32 (2H, d-*pseudo*-t, J = 8.9, 2.2, 2 × Ar-**H**[*o*-NO_2]); FAB MS *m/z* 283 (MH^+, 100%); HRMS calc. for $C_{12}H_{15}N_2O_4S$ 283.0753, found 283.0758

4-Nitro-*N*-[*trans*-2-pyrrolidin-1-ylcyclohexyl]benzenesulfonamide (112)

To a stirred solution of aziridine **111** (0.21 g, 0.73 mmol) in anhydrous THF (4 ml) at RT was added ytterbium (III) trifluoromethanesulfonate (45 mg, 0.07 mmol). Pyrrolidine (0.18 ml, 2.18 mmol) was added dropwise and the reaction was stirred at RT for 15 hours. The solvent was then evaporated *in vacuo* and the residue partitioned between $CHCl_3$ (20 ml) and water (15 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (6% MeOH: 93% $CHCl_3$: 1% NH_4OH) afforded the title product (0.23 g, 88%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.20; ν_{max} (KBr) 1530 (N=O), 1350 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.97-1.21 (4H, m, $N(CH_2)_2(\mathbf{CH_2})_2$), 1.44-1.75 (7H, m, 7 × Cyclohexyl **CH**), 2.04-2.43 (6H, m, $N(\mathbf{CH_2})_2(CH_2)_2$ + 1 × Cyclohexyl **CH**), 2.67 (1H, m, **CH**$NHSO_2Ar$), 8.00 (2H, d-*pseudo*-t, J = 8.8, 2.4, 2 × Ar-**H**[*o*-SO_2]), 8.29 (2H, d-*pseudo*-t, J = 8.8, 2.4, 2 × Ar-**H**[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 21.77, 23.55, 24.15, 24.90, 32.61, 46.75, 55.59, 61.50, 124.19 (Ar-CH), 128.44 (Ar-CH), 146.41 (Ar-C), 149.92 (Ar-C); FAB MS *m/z* 354 (MH^+, 100%); HRMS calc. for $C_{16}H_{24}N_3O_4S$ 354.1488, found 354.1491

4-Nitro-*N*-(3-phenylpropyl)-*N*-[(1*S*,2*R*)-2-pyrrolidin-1-ylcyclohexyl]benzene sulfonamide (113)

To a stirred solution of **112** (0.11 g, 0.30 mmol) in DMF (5 ml) at RT was added potassium carbonate (0.26 g, 0.75 mmol) followed immediately by 1-bromo-3-phenylpropane (0.12 ml, 0.33 mmol). The reaction was stirred at RT for 20 hours then the solvent was evaporated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 ml) and water (10 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 15 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (100%

Hexanes to remove excess bromide then 20% EtOAc: 80% Hexanes) afforded the title product (82 mg, 58%); ν_{max} (KBr) 1521 (N=O), 1349 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.90-2.00 (14H, m, 14 × Alkyl C**H**), 2.30 (4H, m, $N(CH_2)_2(CH_2)_2$), 2.51 (3H, m, $CHN(CH_2)_4$ + $(CH_2)_2CH_2Ph$), 3.10 (2H, t, *J* = 7.7, $NCH_2(CH_2)_2Ph$), 3.57 (1H, td, *J* = 11.1, 3.7, $CHNSO_2Ar$), 7.05-7.24 (5H, m, $(CH_2)_3$**Ph**), 7.95 (2H, d-*pseudo*-t, *J* = 8.9, 2.0, 2 × Ar-**H**[*o*-SO_2]), 8.17 (2H, d-*pseudo*-t, *J* = 8.9, 2.0, 2 × Ar-**H**[*o*-NO_2]); FAB MS *m/z* 472 (MH^+, 50%)

***trans*-*N*-(3-Phenylpropyl)-2-pyrrolidin-1-ylcyclohexanamine (114)**

To a vigorously stirred suspension of potassium carbonate (149 mg, 1.08 mmol) in anhydrous DMF (1 ml) was added benzenethiol (85 µl, 0.72 mmol). The mixture was stirred for 30 minutes before a solution of **113** (85 mg, 0.18 mmol) in anhydrous DMF (2 ml) was added dropwise under an atmosphere of nitrogen. The reaction was stirred at RT for 18 hours and then the solvent was evaporated *in vacuo*. The residue was partitioned between 4:1 $CHCl_3$: EtOH (20 ml) and water (10 ml). The layers were separated and the aqueous layer was extracted with 4:1 $CHCl_3$: EtOH (2 × 15 ml). The combined organic layers were washed with aq. sat. $NaHCO_3$ (20 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (1-5% MeOH: $CHCl_3$: 1% NH_4OH) afforded the title product as a colourless oil (38 mg, 74%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.47; 0.90-1.20 (5H, m, $N(CH_2)_2(CH_2)_2$ + cyclohexyl), 1.54-1.82 (8H, m, 8 × Alkyl C**H**), 1.97 (1H, m, cyclohexyl), 2.21 (1H, td, *J* = 10.4, 4.2, $CHNH(CH_2)_3Ph$), 2.34-2.72 (9H, m, $N(CH_2)_2$ + cyclohexyl), 7.07-7.23 (5H, m, $(CH_2)_3$**Ph**); FAB MS *m/z* 287 (MH^+, 100%)

***N*'-(2,2-Dimethylcyclohexylidene)-4-nitrobenzenesulfonohydrazide (117)**

To a stirred suspension of powdered sodium amide (5.15 g, 132 mmol) in diethyl ether (50 ml) at 0°C was added a solution of 2-methylcyclohexanone (8.0 ml, 66.0 mmol) in diethyl ether (40 ml) dropwise over 1 hour. When the addition was complete, the enolate was allowed to warm to RT and stirred for 16 hours. This was followed by 2 hours at gentle reflux, after which the mixture was cooled to 0°C. Iodomethane (4.5 ml, 72.6 mmol) was added rapidly and the reaction heated to reflux for a further 3 hours. After allowing to cool to RT, the reaction was quenched by

pouring over 100 g of crushed ice. The mixture was subsequently acidified by the addition of aq. 2M HCl (100 ml) and transferred to a separating funnel. The layers were separated and the aqueous layer extracted with diethyl ether (2 × 100 ml). The combined organic layers were washed with aq. 2M sodium thiosulfate (150 ml), then dried ($MgSO_4$), filtered and cautiously evaporated (at 30°C to avoid evaporation of product) to give crude 2,2-dimethylcyclohexanone as a yellow oil. The crude ketone was redissolved in EtOH (80 ml) and *p*-toluenesulfonylhydrazide (12.3 g, 66.0 mmol) added in one portion. The reaction was heated at 60°C for 1.5 hours, before allowing to cool to RT. The mixture was then concentrated *in vacuo* until its volume had been reduced to ~30 ml. The flask was kept in a freezer for 3 days, after which time crystals had been deposited. These were subsequently collected by suction filtration, washed with EtOH (3 × 20ml) and dried under vacuum to afford the title product as colourless prisms (8.42 g, 43%); R_f (50% EtOAc: 50% Hexanes): 0.28

2,2-Dimethylcyclohexene (118)

Tosylhydrazone **117** (1.63 g, 5.54 mmol) was ground to a fine powder and suspended in diethyl ether (10 ml). The mixture was cooled to -78°C and methyllithium (8.0 ml of a 1.6 M solution in diethyl ether, 12.7 mmol) was added dropwise over 15 minutes under an atmosphere of nitrogen. The reaction was subsequently stirred at -78°C for 45 minutes before allowing to slowly warm to RT. During this period, the mixture turned from yellow to deep red accompanied by vigorous evolution of nitrogen, and finally back to yellow again. When the gas evolution had ceased (approximately 2 hours), the reaction was quenched by the cautious dropwise addition of water (20 ml), causing the colour of the reaction to change from yellow to white. The mixture was stirred until two distinct layers had formed, at which point pentane (20 ml) was added. The layers were separated and the aqueous layer further extracted with pentane (2 × 20 ml). Most of the diethyl ether was then removed *in vacuo* and the remaining pentane extracts were dried ($MgSO_4$) and suction filtered through a pad of Celite® to remove residual starting material. The filter pad was washed with pentane (2 × 15 ml) and the filtrate concentrated *in vacuo* to afford the title product as a colourless liquid (0.51 g, 84 %); δ_H (270 MHz, $CDCl_3$): 0.95 (6H, s, *gem*-CH_3), 1.42 (2H, m, $(CH_3)_2CH_2CH_2$), 1.60 (2H, m, $CH_2CH_2CH_2$), 1.91 (2H, m, CH_2CH_2CH=CH), 5.39 (1H, dt, J = 10.2, 2.0,

$(CH_3)_2CH$=CH), 5.52 (1H, dt, J = 9.9, 3.7, CH=C**H**CH_2); δ_C (67.8 MHz, $CDCl_3$): 19.55, 25.16, 29.92, 37.30, 124.57 (CH=CH), 137.85 (CH=CH)

2,2-Dimethyl-7-[(4-nitrophenyl)sulfonyl]-7-azabicyclo[4.1.0]heptane (119)

Copper(II) trifluoromethanesulfonate (0.76 g, 2.09 mmol) and 4Å molecular sieves (1.7 g) were added to a solution of alkene **118** (0.92 g, 8.35 mmol) in anhydrous acetonitrile (30 ml). To this resulting green mixture was added nitrene donor species **110** (5.10 g, 12.5 mmol) portionwise over 4 hours at RT. The reaction was stirred at RT for 16 hours before suction filtering through a pad of Celite®. The filter pad was washed with EtOAc (3 × 30 ml) and the filtrate subsequently washed with aq. saturated $NaHCO_3$ (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid. Column chromatography (15% EtOAc: 85% Hexanes) afforded the title product as white crystals (1.47 g, 57%); R_f (50% EtOAc: 50% Hexanes): 0.51; ν_{max} (KBr) 1532 (N=O), 1351 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.78 (3H, s, *gem*-CH_3), 1.05 (1H, m, $(CH_3)_2CH_2CH_2$), 1.08 (3H, s, *gem*-CH_3), 1.26 (1H, m, $(CH_3)_2CH_2CH_2$), 1.38 (2H, m, $CH_2CH_2CH_2$), 1.76 (1H, m, CH_2CH_2CH), 1.87 (1H, dq, J = 14.8, 5.2, CH_2CH_2CH), 2.76 (1H, d, J = 6.8, $(CH_3)_2CHCH$), 3.25 (1H, ddd, J = 6.8, 5.2, 1.6, CH_2CHCH), 8.19 (2H, m, J = 8.8, 2 × Ar-H[*o*-SO_2]), 8.42 (2H, m, J = 8.8, 2 × Ar-H[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 16.57, 22.14, 26.70, 27.90, 28.92, 33.73, 42.14, 50.52, 124.19 (Ar-CH), 129.25 (Ar-CH), 144.60 (Ar-C), 150.47 (Ar-C); FAB MS *m/z* 310 (M^-, 45%)

***N*-[*trans*-2,2-Dimethyl-6-pyrrolidin-1-ylcyclohexyl]-4-nitrobenzenesulfonamide (120)**

To a stirred solution of **119** (0.35 g, 1.13 mmol) in anhydrous THF (7 ml) was added ytterbium(III) trifluoromethanesulfonate (0.07g, 0.11 mmol) at 0°C. The resulting mixture was stirred at 0°C for 10 minutes before the dropwise addition of pyrrolidine (0.28 ml, 3.38 mmol). The reaction was allowed to warm to RT and then stirred for 24 hours, after which the solvent was removed *in vacuo*. The residue was partitioned between $CHCl_3$ (20 ml) and water (20 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange solid. Column chromatography (100% CH_2Cl_2 then 2% MeOH: 1% NH_4OH: 97% CH_2Cl_2)

afforded the title product as fine yellow prisms (0.40 g, 92%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.33; ν_{max} (KBr) 1528 (N=O), 1349 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.72 (3H, s, *gem*-CH_3), 0.74 (3H, s, *gem*-CH_3), 1.27 (4H, m, $(CH_3)_2CH_2CH_2CH_2$), 1.52 (4H, m, py-$N(CH_2)_2$), 1.59 (1H, m, CH_2CH_2CH), 1.77 (1H, br-d, J = 12.1, CH_2CH_2CH), 2.47 (4H, m, py-$N(CH_2)_2(CH_2)_2$), 2.60 (1H, dd, J = 11.2, 3.5), 3.16 (1H, d, J = 11.2), 5.44 (1H, br-s, NH), 8.07 (2H, d, J = 8.7, 2 × Ar-H[*o*-SO_2]), 8.27 (2H, d, 8.7, 2 × Ar-H[*o*-NO_2]); δ_C (67.8 MHz, $CDCl_3$): 19.62, 20.51, 22.71, 23.65, 30.98, 36.59, 39.57, 46.95, 57.92, 64.67, 123.87 (Ar-CH), 127.93 (Ar-CH), 148.43 (Ar-C), 149.44 (Ar-C); FAB MS *m/z* 382 (M^+, 100%)

_N_-[*trans*-2,2-Dimethyl-6-pyrrolidin-1-ylcyclohexyl]-4-nitro-_N_-[(_E_)-3-phenylprop-2-enyl]benzenesulfonamide (121)

To a stirred solution of **120** (0.29 g, 0.75 mmol) in anhydrous DMF (10 ml) was added cesium carbonate (0.49 g, 1.49 mmol), causing the reaction colour to change from yellow to deep red as deprotonation of the sulfonamide occurred. Cinnamyl bromide (0.22 g, 1.12 mmol) was then added in one portion and the reaction stirred at RT for 20 hours, during which time the colour became yellow again. The solvent was removed *in vacuo* and the resulting residue partitioned between CH_2Cl_2 (20 ml) and water (15 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow solid (0.49 g). Column chromatography (100% Hexanes to elute residual cinnamyl bromide then 10% EtOAc: 90% Hexanes) gave the title product as a yellow powder (0.34 g, 94%); R_f (50% EtOAc: 50% Hexanes): 0.54; m.p. 164-166 °C; ν_{max} (KBr) 1525 (N=O), 1345 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.02 (3H, s, *gem*-CH_3), 1.14 (3H, s, *gem*-CH_3), 1.44 (4H, m, $(CH_3)_2CH_2CH_2CH_2$), 1.70 (4H, m, J = 6.4, py-$N(CH_2)_2(CH_2)_2$), 1.76 (1H, m, CH_2CH_2CH), 2.58 (2H, m, J = 8.0, py-$N(CH_2)_2(CH_2)_2$), 2.79 (2H, m, J = 8.0, py-$N(CH_2)_2(CH_2)_2$), 2.98 (1H, dd, J = 10.8, 7.2, CH_2CHCH), 3.92 (1H, ddd, J = 16.4, 5.6, 1.6, CH_2CH=CH), 4.06 (1H, d, J = 11.6, $(CH_3)_2CHCH$), 4.13 (1H, dd, J = 16.4, 8.0, CH_2CH=CH), 5.85 (1H, ddd, J = 16.4, 8.0, 5.6, CH_2CH=CH), 6.42 (1H, d, J = 16.4, CH=CHPh), 7.11 (2H, dd, J = 8.0, 1.6, Ar-H[*o*-CHCH]), 7.28 (3H, m, Ar-H[*m,p*-CHCH]), 8.02 (2H, d, J = 8.8, 2 × Ar-H[*o*-SO_2]), 8.07 (2H, d, J = 8.8, 2 × Ar-H[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 20.88, 21.96, 23.59, 24.57, 31.96, 42.37, 47.62,

48.20, 54.95, 68.72, 123.25 (Ar-CH), 126.08 (Ar-CH), 126.73 (Ar-CH), 128.07 (Ar-CH), 128.67 (Ar-CH), 130.03 (Ar-CH), 132.58 (Ar-CH), 136.23 (Ar-C), 148.25 (Ar-C), 149.07 (Ar-C); FAB MS *m/z* 498 (M^+, 50%)

trans-2,2-Dimethyl-_N_-[(_E_)-3-phenylprop-2-enyl]-6-pyrrolidin-1-ylcyclo hexanamine (122)

To a stirred solution of **121** (0.27 g, 0.56 mmol) in anhydrous DMF (10 ml) at RT was added lithium hydroxide monohydrate (0.12 g, 2.78 mmol) followed by mercaptoacetic acid (120 µl, 1.67 mmol). After stirring for several minutes at RT, the colour of the reaction was observed to change from yellow to red. TLC analysis after 24 hours showed incomplete consumption of **121**. The system was subsequently heated at 50°C for a further 3 hours, after which time additional lithium hydroxide monohydrate (70 mg, 1.67 mmol) and mercaptoacetic acid (78 µl, 1.11 mmol) was added to the reaction. After heating at 60°C for a further 16 hours, the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 ml) and aq. 2M NaOH (15 ml). The layers were separated and the aqueous layer extracted with EtOAc (2 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Column chromatography (1-2% MeOH: $CHCl_3$: 1% NH_4OH) afforded the title product as a colourless oil (92 mg, 53%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.20; ν_{max} (film) 1612, 1513 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.91 (3H, s, *gem*-CH_3), 1.03 (3H, s, *gem*-CH_3), 1.09-1.21 (2H, m, cyclohexyl), 1.31-1.35 (1H, m, cyclohexyl), 1.41 (1H, tt, J = 13.2, 3.6, cyclohexyl), 1.61 (1H, dt, J = 10.0, 3.6, cyclohexyl), 1.63-1.73 (4H, m, $N(CH_2)_2(CH_2)_2$), 1.74-1.80 (1H, m, cyclohexyl), 2.08 (1H, d, J = 11.2, $C(CH_3)_2CHCH$), 2.50-2.63 (5H, m, $N(CH_2)_2$ + CH_2CHCH), 3.36 (1H, dd, J = 13.6, 6.8, $NHCH_2CH$=CH), 3.55 (1H, dd, J = 13.6, 5.6, $NHCH_2CH$=CH), 6.30 (1H, dt, J = 15.6, 6.4, CH_2CH=CH), 6.49 (1H, d, J = 16.0, CH=CHPh), 7.19 (1H, t, J = 7.6, Ar-H[*p*-CH=CH]), 7.29 (2H, t, J = 7.6, 2 × Ar-H[*m*-CH=CH]), 7.36 (2H, d, J = 6.8, 2 × Ar-H[*o*-CH=CH]); δ_C (100 MHz, $CDCl_3$): 19.84, 20.98, 22.56, 23.74, 31.64, 37.00, 40.15, 47.12, 54.83, 58.10, 68.39, 126.18 (2 × Ar-CH), 127.07 (Ar-CH), 128.44 (2 × Ar-CH), 129.78 (Ar-CH), 130.42 (Ar-CH), 137.41 (Ar-C); FAB MS *m/z* 313 (MH^+, 100%); HRMS submitted

trans-1,1-Dimethyl-2-{[(2-nitrophenyl)sulfonyl]amino}-3-pyrrolidin-1-yl-1,2,3,4-tetrahydronaphthalen-7-yl 7-nitrobenzenesulfonate (124) from 68

To a stirred solution of aziridine **68** (0.61 g, 3.21 mmol) and triethylamine (1.34 ml, 9.64 mmol) in CH_2Cl_2 (20 ml) at RT was added 2-nitrobenzenesulfonyl chloride (2.14 g, 9.64 mmol) in small portions. The reaction was stirred at RT for 16 hours and then quenched by the cautious addition of water (20 ml). The resulting two-phase system was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an orange solid. Column chromatography (30-50% EtOAc: Hexanes) afforded **123** as an orange solid (1.56 g, 87%). Aziridine **123** (0.45 g, 0.81 mmol) was redissolved in anhydrous dimethylsulfoxide (20 ml) and ytterbium (III) trifluoromethanesulfonate (0.10 g, 0.16 mmol) was added. The mixture was stirred for 10 minutes before the dropwise addition of pyrrolidine (0.27 ml, 3.23 mmol). The reaction was stirred at RT for 16 hours and then diluted with water (20 ml) and ethyl acetate (40 ml). The resulting two-phase system was separated and the aqueous layer extracted with ethyl acetate (2 × 40 ml). The combined organic layers were washed with water (2 × 50 ml), brine (50 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (1% MeOH: $CHCl_3$: 1% NH_4OH) afforded the title product as a yellow oil (0.49 g, 95%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.42; δ_H (270 MHz, $CDCl_3$): 1.01 (3H, s, *gem*-CH_3), 1.17-1.37 (4H, m, Py-N$(CH_2)_2(CH_2)_2$), 1.24 (3H, s, *gem*-CH_3), 2.33 (4H, m, Py-N$(CH_2)_2(CH_2)_2$), 2.75-3.04 (3H, m, 4-CH_2 + 3-CH), 3.52 (1H, d, J = 9.4, 2-CH), 6.92-7.02 (3H, m, 5-ArH + 6-ArH + 8-ArH), 7.62-7.87 (6H, m, 6 × ArH), 7.90 (1H, m, Ar-H[*o*-NO_2]), 8.09 (1H, m, Ar-H[*o*-NO_2])

7-Methoxy-1,1-dimethyl-1-[(4-nitrophenyl)sulfonyl]-1,2,3,4-tetrahydronaphtho[2,3-*b*]azirene (126)

To a stirred solution of aziridine **67** (0.54 g, 2.66 mmol) in CH_2Cl_2 (30 ml) was added triethylamine (1.11 ml, 7.97 mmol) and 4,4-dimethylaminopyridine (30 mg, 0.27 mmol). The mixture was cooled to 0°C before the dropwise addition of 4-nitrobenzenesulfonyl chloride (0.65 g, 2.92 mmol) in CH_2Cl_2 (5 ml). The reaction was stirred at 0°C for 1 hour then allowed to warm to RT and stirred for a further 18 hours, after which time the reaction was quenched by the cautious addition of aq.

saturated $NaHCO_3$ (20 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography (10-15% EtOAc: Hexanes) afforded the title product as a white powder (0.70 g, 68%); R_f (50% EtOAc: 50% Hexanes): 0.64; m.p. 140-142 °C; ν_{max} (KBr) 1532 (N=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.22 (6H, s, *gem*-(CH_3)$_2$), 3.07 (1H, d, *J* = 7.2, 2-C**H**), 3.13 (2H, dd, *J* = 6.0, 2.0, 4-C**H**$_2$), 3.53 (1H, dt, *J* = 7.2, 2.0, 3-C**H**), 3.75 (3H, s, 7-OCH_3), 6.67 (1H, dd, *J* = 8.4, 2.8, 6-ArH), 6.89 (1H, d, *J* = 8.4, 5-ArH), 8.06 (2H, d, *J* = 8.8, 2 × Ar-H[*o*-SO_2]), 8.31 (2H, d, *J* = 8.8, 2 × Ar-H[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 26.72, 27.69, 29.11, 34.92, 41.09, 51.14, 55.16, 111.40 (Ar-CH), 111.49 (Ar-CH), 121.40 (Ar-C), 124.11 (Ar-CH), 129.23 (Ar-CH), 129.96 (Ar-CH), 141.92 (Ar-C), 144.27 (Ar-C), 150.44 (Ar-C), 158.67 (Ar-C); FAB MS *m/z* 389 (MH^+, 60%); HRMS submitted

N-[*trans*-7-Methoxy-1,1-dimethyl-3-pyrrolidin-1-yl-1,2,3,4-tetrahydro naphthalen-2-yl]-4-nitrobenzenesulfonamide (127)

To a stirred solution of aziridine **126** (0.31 g, 0.79 mmol) in anhydrous THF (7 ml) was added ytterbium(III) trifluoromethanesulfonate (49 mg, 0.08 mmol). The mixture was stirred at RT for 5 minutes, before the dropwise addition of pyrrolidine (0.20 ml, 2.38 mmol). The reaction was heated at reflux for 42 hours, then allowed to return to RT. Water (10 ml) was added and the THF evaporated *in vacuo*. The resulting suspension was extracted with 3:1 $CHCl_3$: MeOH (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Column chromatography (50% EtOAc: 50% Hexanes to elute trace of starting material then 100% EtOAc) afforded the title product as a yellow solid (0.34 g, 93%); ν_{max} (KBr) 1530 (N=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.04 (3H, s, *gem*-CH_3), 1.15 (3H, s, *gem*-CH_3), 1.75 (4H, m, py-N(CH_2)$_2$(CH_2)$_2$), 2.58 (2H, m, py-N(CH_2)$_2$(CH_2)$_2$), 2.68 (2H, m, py-N(CH_2)$_2$(CH_2)$_2$), 2.85 (2H, m, 4-C**H**$_2$), 3.04 (1H, td, *J* = 10.2, 5.9, 3-C**H**), 3.66 (1H, d, *J* = 10.4, 2-C**H**), 3.74 (3H, s, 7-OCH_3), 6.68 (1H, dd, *J* = 8.2, 2.5, 6-ArH), 6.73 (1H, d, *J* = 2.5, 8-ArH), 6.96 (1H, d, *J* = 8.2, 5-ArH), 8.11 (2H, d, *J* = 8.9, Ar-H[*o*-SO_2]), 8.35 (2H, d, *J* = 8.9, Ar-H[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 23.59, 25.90, 26.96, 29.72, 41.22, 47.37, 55.23, 55.39, 63.41, 111.84 (Ar-CH), 112.53 (Ar-CH), 124.09 (Ar-CH), 125.28 (Ar-C), 128.12

(Ar-CH), 130.03 (Ar-CH), 144.98 (Ar-C), 148.02 (Ar-C), 149.66 (Ar-C), 158.22 (Ar-C); FAB MS submitted

_N_-[*trans*-7-Methoxy-1,1-dimethyl-3-pyrrolidin-1-yl-1,2,3,4-tetrahydro naphthalen-2-yl]-4-nitro-_N_-[(_E_)-3-phenylprop-2-enyl]benzenesulfonamide (128)

To a vigorously stirred solution of **127** (0.53 g, 1.15 mmol) in anhydrous acetonitrile (30 ml) was added freshly powdered potassium carbonate (0.32 g, 2.31 mmol) and 18-crown-6 (30mg, 0.12 mmol) at RT. The mixture became red as deprotonation of the sulfonamide occurred. After stirring for 5 minutes, cinnamyl bromide (0.27 g, 1.38 mmol) was added in one portion and the reaction stirred vigorously at RT for 30 hours. The solvent was then evaporated *in vacuo* and the residue subsequently partitioned between water (10 ml) and $CHCl_3$ (20 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (0-15% EtOAc: Hexanes) afforded the title product as a yellow powder (0.37 g, 55%); R_f (50% EtOAc: 50% Hexanes): 0.58; m.p. 161-163 °C; ν_{max} (KBr) 1526 (N=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.38 (3H, s, *gem*-CH_3), 1.54 (3H, s, *gem*-CH_3), 1.85 (4H, m, py-$N(CH_2)_2(CH_2)_2$), 2.64 (2H, m, py-$N(CH_2)_2(CH_2)_2$), 2.77 (1H, dd, J = 14.4, 6.0, 4-CH), 2.90 (2H, m, py-$N(CH_2)_2(CH_2)_2$), 2.98 (1H, d, J = 14.8, 4-CH), 3.17 (1H, m, 3-CH), 3.36 (1H, dd, J = 16.4, 3.6, CH_2CH=CH), 3.78 (3H, s, 7-OCH_3), 3.97 (1H, dd, J = 16.4, 8.4, CH_2CH=CH), 4.50 (1H, d, J = 8.0, 2-CH), 5.35 (1H, ddd, J = 16.0, 8.8, 5.2, CH_2CH=CH), 6.03 (1H, d, J = 16.0, CH_2CH=CH), 6.70 (1H, dd, J = 8.2, 2.4, 6-ArH), 6.84 (2H, dd, J = 7.2, 4.0, 2 × Ar-H[*o*-CH=CH]), 6.89 (1H, d, J = 2.8, 8-ArH), 7.04 (1H, d, J = 8.2, 5-ArH), 7.15 (3H, m, 2 × Ar-H[*m*-CH=CH] + Ar-H[*p*-CH=CH]), 7.99 (2H, d, J = 8.8, 2 × Ar-H[*o*-SO_2]), 8.28 (2H, d, J = 8.8, 2 × Ar-H[*o*-NO_2]), δ_C (100 MHz, $CDCl_3$): 24.11, 24.27, 25.43, 30.69, 40.44, 47.64, 47.68, 55.19, 60.02, 68.01, 110.50 (Ar-CH), 110.85 (Ar-CH), 123.03 (Ar-CH), 124.48 (Ar-CH), 125.83 (CH=CH), 127.64 (Ar-C), 128.10 (Ar-CH), 128.47 (Ar-CH), 2 × 129.67 (Ar-CH), 133.54 (CH=CH), 135.51 (Ar-C), 145.95 (Ar-C), 149.02 (Ar-C), 149.20 (Ar-C), 158.92 (Ar-C); FAB MS *m/z* 577 (MH^+, 40%); HRMS calc for $C_{32}H_{37}N_3O_5S$ 576.2532, found 576.2570

***trans*-7-Methoxy-1,1-dimethyl-*N*-[(*E*)-3-phenylprop-2-enyl]-3-pyrrolidin-1-yl-1,2,3,4-tetrahydronaphthalen-2-amine (129)**

To a vigorously stirred suspension of potassium carbonate (0.50 g, 3.65 mmol) in anhydrous DMF (3 ml) was added benzenethiol (0.25 ml, 2.43 mmol) dropwise at RT under an atmosphere of nitrogen. The thiolate mixture was stirred for 10 minutes, then a solution of **128** (0.35 g, 0.61 mmol) in anhydrous DMF (4 ml) was added dropwise over 5 minutes. The reaction was observed to immediately change colour from yellow to dark brown. After stirring at RT for 48 hours, the solvent was evaporated *in vacuo* and the residue partitioned between 4:1 $CHCl_3$: EtOH (20 ml) and water (15 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$: EtOH (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Column chromatography (1% NEt_3: 99% CH_2Cl_2) afforded the title product as a yellow oil (0.18 g, 76%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.27; ν_{max} (film) 1504, 1494 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.23 (3H, s, *gem*-CH_3), 1.45 (3H, s, *gem*-CH_3), 1.75 (4H, m, py-N$(CH_2)_2$($\mathbf{CH_2}$)$_2$), 2.53 (1H, d, J = 10.8, 2-C**H**), 2.66 (4H, m, py-N($\mathbf{CH_2}$)$_2$$(CH_2)_2$), 2.85 (2H, m, 4-$\mathbf{CH_2}$), 3.05 (1H, td, J = 10.8, 5.6, 3-C**H**), 3.46 (1H, ddd, J = 13.6, 6.4, 1.2, $\mathbf{CH_2}$CH=CH), 3.62 (1H, dd, J = 13.6, 6.0, $\mathbf{CH_2}$CH=CH), 3.79 (3H, s, 7-O$\mathbf{CH_3}$), 6.35 (1H, dt, J = 16.0, 6.0, CH_2C**H**=CH), 6.56 (1H, d, J = 15.6, CH_2CH=C**H**), 6.68 (1H, dd, J = 8.4, 2.4, 6-Ar**H**), 6.89 (1H, d, J = 2.4, 8-Ar**H**), 6.98 (1H, d, J = 8.4, 5-Ar**H**), 7.21 (1H, tt, J = 7.2, 1.6, Ar-**H**[*p*-CH=CH]), 7.30 (2H, t, J = 7.2, 2 × Ar-**H**[*m*-CH=CH]), 7.38 (2H, dt, J = 7.2, 1.6, 2 × Ar-**H**[*o*-CH=CH]), δ_C (100 MHz, $CDCl_3$): 23.77, 26.08, 26.48, 28.91, 41.73, 47.45, 55.02, 55.22, 55.48, 66.79, 111.26 (CH=CH), 111.97 (CH=CH), 126.19 (Ar-CH), 126.54 (Ar-C), 127.113 (Ar-CH), 128.46 (Ar-CH), 129.58 (Ar-CH), 129.80 (Ar-CH), 130.32 (Ar-CH), 137.40 (Ar-C), 147.17 (Ar-C), 157.84 (Ar-C); FAB MS *m/z* 391 (M^+, 100%); HRMS submitted

***N*-{*trans*-3-[(Cyclopropylmethyl)amino]-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}-4-nitrobenzenesulfonamide (130)**

To a stirred solution of aziridine **126** (0.58 g, 1.49 mmol) in anhydrous THF (15 ml) was added ytterbium(III) trifluoromethanesulfonate (93 mg, 0.15 mmol) at RT. The mixture was stirred for 5 minutes before the dropwise addition of (aminomethyl)cyclopropane (0.39 ml, 4.48 mmol), after which the reaction was

heated to gentle reflux for 5 days. The mixture was allowed to return to RT and the THF subsequently removed *in vacuo*. The resulting residue was partitioned between 4:1 $CHCl_3$: EtOH (30 ml) and water (20 ml). The layers were separated and the aqueous layer extracted with 4:1 $CHCl_3$: EtOH (2 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (30% EtOAc: 70% Hexanes to elute residual starting material, then 80% EtOAc: 20% Hexanes) afforded the title product as a yellow solid (0.57 g, 83%); m.p. 174-176 °C; ν_{max} (KBr) 1609 (N=O), 1531, 1506, 1451 cm^{-1}; δ_H (270 MHz, $CDCl_3$): -0.05 (2H, m, $CH(CH_2)_2$), 0.35 (2H, m, $CH(CH_2)_2$), 1.15 (3H, s, *gem*-CH_3), 1.33 (3H, s, *gem*-CH_3), 2.26-2.41 (3H, m, $CH_2CH(CH_2)_2$ + 4-CH), 2.76 (1H, td, J = 10.4, 4.9, 3-CH), 3.13 (1H, dd, J = 15.8, 4.9, 4-CH), 3.30 (1H, d, J = 10.4, 2-CH), 3.76 (3H, s, 7-OCH_3), 6.67 (1H, dd, J = 8.4, 2.6, 6-ArH), 6.80 (1H, d, J = 2.6, 8-ArH), 6.91 (1H, d, J = 8.4, 5-ArH), 8.09 (2H, d, J = 9.2, 2 × Ar-H[*o*-SO_2]), 8.32 (2H, d, J = 9.2, 2 × Ar-H[*o*-NO_2]); δ_C (68 MHz, $CDCl_3$): 3.44, 11.55, 26.46, 28.73, 37.15, 40.97, 52.47, 53.86, 55.38, 65.22, 112.18 (Ar-CH), 112.46 (Ar-CH), 124.18 (Ar-CH), 124.76 (Ar-C), 128.81 (Ar-CH), 129.82 (Ar-CH), 145.17 (Ar-C), 147.10 (Ar-C), 149.88 (Ar-C), 158.38 (Ar-C); FAB MS *m/z* 461 (MH^+, 100%); HRMS calc for $C_{23}H_{29}N_3O_5S$ 460.1906, found 460.1882

_N_-[*trans*-7-Methoxy-1,1-dimethyl-3-(methylamino)-1,2,3,4-tetrahydro naphthalen-2-yl]-4-nitrobenzenesulfonamide (131)

Nosyl aziridine **126** (0.73 g, 1.88 mmol) was dissolved in methylamine solution (14.1 ml, 2.0M in THF, 28.2 mmol) at RT. Ytterbium (III) trifluoromethanesulfonate (0.35 g, 0.56 mmol) was added and the reaction was subsequently heated to reflux for 24 hours. After this time, a further 14.1 ml of methylamine solution was added and heating continued for another 24 hours. The addition was repeated twice more (total volume of methylamine solution added = 56.4 ml, total reaction time = 96 hours), after which the reaction was allowed to cool to RT. The solvent and excess methylamine was evaporated *in vacuo* and the residue partitioned between 4:1 $CHCl_3$: EtOH (60 ml) and water (40 ml). The layers were separated and the aqueous layer was extracted with 4:1 $CHCl_3$: EtOH (2 × 60 ml). The combined organic layers were washed with brine (30 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Column chromatography

(100% CH_2Cl_2 to elute residual starting material then 2% MeOH: 97% CH_2Cl_2: 1% NH_4OH) afforded the title product as a yellow solid (0.29 g, 37%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.34; m.p. 158-161 °C; ν_{max} (KBr) 1528 (N=O), 1348 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.13 (3H, s, *gem*-CH_3), 1.18 (3H, s, *gem*-CH_3), 2.34 (3H, s, 3-NHCH_3), 2.44 (1H, dd, *J* = 15.6, 10.4, 4-C**H**), 2.70 (1H, td, *J* = 10.4, 5.2, 3-C**H**), 3.22 (1H, dd, *J* = 15.6, 5.2, 4-C**H**), 3.36 (1H, d, *J* = 10.4, 2-C**H**), 3.76 (3H, s, 7-OCH_3), 6.69 (1H, dd, *J* = 8.4, 2.4, 6-Ar**H**), 6.77 (1H, d, *J* = 2.4, 8-Ar**H**), 6.95 (1H, d, *J* = 8.4, 5-Ar**H**), 8.08 (2H, d-*pseudo*-t, *J* = 8.8, 2.4, 2 × Ar-**H**[*o*-SO_2]), 8.34 (2H, d-*pseudo*-t, *J* = 8.8, 2.4, 2 × Ar-**H**[*o*-NO_2]); δ_C (100 MHz, $CDCl_3$): 26.29, 28.52, 33.63, 36.00, 40.71, 55.25, 55.56, 65.19, 112.04 (Ar-CH), 112.33 (Ar-CH), 124.03 (Ar-CH), 124.66 (Ar-C), 128.53 (Ar-CH), 129.82 (Ar-CH), 144.85 (Ar-C), 147.15 (Ar-C), 149.78 (Ar-C), 158.28 (Ar-C); EI MS *m/z* 419 (M^+, 25%)

_N_-(*trans*-3-{(Cyclopropylmethyl)[(4-nitrophenyl)sulfonyl]amino}-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-nitrobenzenesulfonamide (132)

To a stirred solution of **130** (0.55 g, 1.20 mmol), triethylamine (0.50 ml, 3.59 mmol) and 4,4-dimethylaminopyridine (30 mg, 0.24 mmol) in CH_2Cl_2 (20 ml) at RT was added 4-nitrobenzenesulfonyl chloride (0.32 g, 1.44 mmol) in small portions. The reaction was stirred at RT for 18 hours then quenched by the cautious addition of water (15 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (30% EtOAc: 70% Hexanes) afforded the title product as a yellow powder (0.71 g, 92%); R_f (50% EtOAc: 50% Hexanes): 0.59; m.p. 212-214 °C; ν_{max} (KBr) 1530 (N=O), 1350 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.17 (1H, m) + 0.53 (3H, m, $CH_2CH(CH_2)_2$), 0.80 (1H, m, $CH_2CH(CH_2)_2$), 2.70 (1H, dd, *J* = 15.6, 4.4, 4-C**H**), 3.09-3.19 (2H, m, $CH_2CH(CH_2)_2$), 3.35 (1H, dd, *J* = 15.6, 4.4, 4-C**H**), 3.73 (3H, s, 7-OCH_3), 3.85 (1H, dd, *J* = 11.2, 9.2, 2-C**H**), 4.04-4.13 (1H, m, 3-C**H**), 5.72 (1H, d, *J* = 9.2, N-**H**), 6.66 (1H, dd, *J* = 8.4, 2.4, 6-Ar**H**), 6.74 (1H, d, *J* = 2.4, 8-Ar**H**), 6.84 (1H, d, *J* = 8.4, 5-Ar**H**), 8.11 (4H, overlap br-d, *J* = 8.4, 4 × Ar-**H**[*o*-SO_2]), 8.32 (2H, d-*pseudo*-t, *J* = 8.8, 2.0, 2 × Ar-**H**[*o*-NO_2] on secondary sulfonamide), 8.35 (2H, dd, *J* = 8.8, 2.4, 2 × Ar-**H**[*o*-NO_2] on tertiary sulfonamide); δ_C (100 MHz, $CDCl_3$): 3.47, 7.04, 11.52, 25.87, 28.94, 34.82, 41.97,

48.84, 54.63, 55.20, 61.35, 112.33 (Ar-CH), 112.58 (Ar-CH), 123.13 (Ar-C), 124.29 (Ar-CH), 124.35 (Ar-CH), 128.01 (Ar-CH), 128.13 (Ar-CH), 129.59 (Ar-CH), 144.07 (Ar-C), 147.44 (Ar-C), 147.65 (Ar-C), 149.75 (Ar-C), 149.80 (Ar-C), 159.59 (Ar-C); EI MS submitted

tert-Butyl-cyclopropylmethyl(_trans_-6-methoxy-4,4-dimethyl-3-{[(4-nitro phenyl)sulfonyl]amino}-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (134)

To a stirred solution of **130** (0.38 g, 0.83 mmol), triethylamine (0.35 ml, 2.48 mmol) and 4,4-dimethylaminopyridine (10 mg, 0.08 mmol) in CH_2Cl_2 (15 ml) was added di-*tert*-butyl dicarbonate (0.20 g, 0.91 mmol) in one portion at RT. After stirring at RT for 24 hours, water (15 ml) was added and the two phase system was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml) and the combined organic layers were subsequently washed with aq. 1M HCl (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (10-15% EtOAc: Hexanes) afforded the title product as a yellow solid (0.28 g, 61%); R_f (50% EtOAc: 50% Hexanes): 0.61; m.p. 174-176 °C; ν_{max} (KBr) 1695 and 1655 (C=O), 1533 (N=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.21 (1H, m, $CH_2CH(CH_2)_2$), 0.48 (1H, m, $CH_2CH(CH_2)_2$), 0.53 (2H, m, $CH_2CH(CH_2)_2$), 0.94 (3H, s, *gem*-CH_3), 1.00 (1H, m, $CH_2CH(CH_2)_2$), 1.14 (3H, s, *gem*-CH_3), 1.54 (9H, s, Boc-$(CH_3)_3$), 3.00-3.12 (3H, m, $CH_2CH(CH_2)_2$ + 4-CH), 3.24 (1H, dd, J = 15.3, 7.2, 4-CH), 3.74 (3H, s, 7-OCH_3), 4.57 (1H, td, J = 10.9, 6.7, 3-CH), 5.52 (1H, d, J = 10.8, 2-CH), 6.69 (2H, m, 6-ArH + 8-ArH), 6.97 (1H, d, J = 8.4, 5-ArH), 8.00 (2H, d, J = 8.9, 2 × Ar-H[*o*-SO_2]), 8.32 (2H, d, J = 8.9, 2 × Ar-H[*o*-NO_2]); δ_C (68 MHz, $CDCl_3$): 4.76, 12.18, 26.41, 28.63, 28.83, 34.78, 41.57, 47.93, 51.38, 55.32, 63.98, 81.09, 112.14 (Ar-CH), 112.55 (Ar-CH), 124.35 (Ar-CH), 124.73 (Ar-C), 127.95 (Ar-CH), 129.86 (Ar-CH), 144.41 (Ar-C), 148.07 (Ar-C), 149.77 (Ar-C), 158.35 (Ar-C), 159.23 (C=O); FAB MS *m/z* 561 (MH^+, 50%), HRMS submitted

tert-Butyl-cyclopropylmethyl(_trans_-7-methoxy-1,1-dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydronaphthalen-3-yl)carbamate (135)

To a vigorously stirred suspension of lithium hydroxide monohydrate (0.15 g, 3.57 mmol) in anhydrous DMF (2 ml) was added mercaptoacetic acid (0.13 ml, 1.79 mmol) dropwise at RT. The mixture was stirred for 5 minutes before a solution of

134 (0.25 g, 0.45 mmol) in anhydrous DMF (4 ml) was added dropwise. The reaction was heated at 70°C under an atmosphere of nitrogen for 2 hours then allowed to cool to RT. The solvent was then evaporated *in vacuo* and the residue partitioned between aq. 1M NaOH (20 ml) and $CHCl_3$ (30 ml). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude amine. Column chromatography (20-30% EtOAc: Hexanes) afforded a colourless oil (80 mg) which NMR showed to be a mixture of the desired product and a slightly more polar contaminant. R_f (50% EtOAc: 50% Hexanes): 0.29. The crude amine was subsequently redissolved in anhydrous MeOH (4 ml) and *trans*-cinnamaldehyde (32 µl, 0.26 mmol) was added. The reaction was stirred under an atmosphere of nitrogen for 18 hours at RT then cooled to 0°C. Sodium borohydride (32 mg, 0.85 mmol) was added in two portions and the resulting mixture stirred at 0°C for 1 hour, then at RT for a further 2 hours. The reaction was quenched by the dropwise addition of aq. sat. $NaHCO_3$ (2 ml), followed by water (5 ml). CH_2Cl_2 (10 ml) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (15% EtOAc: 85% Hexanes) afforded the title product as a colourless oil (75 mg, 34% over two steps). R_f (50% EtOAc: 50% Hexanes): 0.63; δ_H (270 MHz, $CDCl_3$): 0.15-0.38 (2H, m, $CH_2CH(CH_2)_2$), 0.52 (2H, d, J = 8.2, $CH_2CH(CH_2)_2$), 1.04 (1H, m, $CH_2CH(CH_2)_2$), 1.20 (3H, s, *gem*-CH_3), 1.41 (3H, s, *gem*-CH_3), 1.46 (3H, s, Boc-CH_3), 1.49 (6H, s, 2 × Boc-CH_3), 2.96-3.51 (7H, m, alkyl), 3.60 (1H, dd, J = 13.3, 5.7, 3-CH), 6.26 (1H, dt, J = 15.8, 5.7, CH_2CH=CH), 6.49 (1H, d, J = 15.6, CH=CHPh), 6.66-6.71 (1H, m, 6-ArH), 6.86 (1H, s, 8-ArH), 6.94 (1H, d, J = 7.2, 5-ArH), 7.16-7.37 (5H, m, 5 × ArH); δ_C (68 MHz, $CDCl_3$): 4.50, 11.86, 25.87, 26.00, 27.95, 28.36, 28.68, 42.16, 53.60, 55.33, 64.75, 65.51, 80.04 (Boc-C), 111.58 (Ar-CH), 112.33 (Ar-CH), 112.56 (Ar-CH), 125.86 (Ar-C), 126.31 (Ar-CH), 127.25 (Ar-CH), 128.58 (Ar-CH), 129.25 (Ar-C), 129.53 (Ar-CH), 130.09 (Ar-CH), 137.35 (Ar-C), 146.86 (Ar-C), 157.90 (C=O); FAB MS *m/z* 491 (MH^+, 100%); HRMS submitted

_N_-(Cyclopropylmethyl)-_N_-(*trans*-7-methoxy-1,1-dimethyl-2-{[(_E_)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydronaphthalen-3-yl)amine (136)

To a stirred solution of **135** (75 mg, 0.15 mmol) in $CHCl_3$ (7 ml) was added trifluoroacetic acid (0.33 ml, 4.58 mmol) dropwise at RT. The reaction was stirred at RT for 48 hours, after which the solvent and excess trifluoroacetic acid were evaporated *in vacuo*. The residue was basified to pH 10 with triethylamine before partitioning between 4:1 $CHCl_3$: EtOH (20 ml) and water (10 ml). The layers were separated and the aqueous layer extracted with 4:1 $CHCl_3$: EtOH (2 × 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product (as an approximately 3:4 mixture of triethylamine: product) as a beige foam (57mg, 96%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.56; ν_{max} (film) 1613, 1496, 1450 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.36 (1H, m, $CH(CH_2)_2$), 0.42 (1H, m, $CH(CH_2)_2$), 0.67 (2H, m, $CH(CH_2)_2$), 1.17 (3H, s, *gem*-CH_3), 1.27 (1H, m, $CH_2CH(CH_2)_2$), 1.49 (3H, s, *gem*-CH_3), 2.74 (1H, dd, J = 13.0, 8.0, 4-C**H**), 3.10-3.19 (3H, m, $CH_2CH(CH_2)_2$ + 2-C**H**), 3.24 (1H, dd, J = 13.0, 7.2, 4-C**H**), 3.54 (1H, m, 3-C**H**), 3.76 (3H, s, 7-OCH_3), 3.78 (2H, m, CH_2CH=CH), 6.38 (1H, dt, J = 16.0, 5.6, CH_2CH=CH), 6.59 (1H, d, J = 16.0, CH=C**H**Ph), 6.69 (1H, dd, J = 8.0, 2.4, 6-Ar**H**), 6.80 (1H, d, J = 2.4, 8-Ar**H**), 6.95 (1H, d, J = 8.0, 5-Ar**H**), 7.18-7.32 (3H, m, 2 × Ar-**H**[*m*-CH=CH] + Ar-**H**[*p*-CH=CH]), 7.38 (2H, d, J = 7.2, 2 × Ar-**H**[*o*-CH=CH]); δ_C (100 MHz, $CDCl_3$): 3.96, 4.67, 7.99, 25.75, 28.43, 31.04, 40.75, 49.58, 53.38, 55.22, 55.64, 63.97, 112.09 (Ar-CH), 112.13 (Ar-CH), 126.34 (Ar-CH), 127.44 (Ar-C), 127.61 (Ar-CH), 128.55 (Ar-CH), 130.13 (Ar-CH), 131.69 (Ar-CH), 136.62 (Ar-C), 144.84 (Ar-C), 158.44 (Ar-C); FAB MS *m/z* 391 (MH^+, 90%); HRMS submitted

(_E_)-_N_-(4-Methoxybenzyl)-3-phenylprop-2-en-1-amine (137)

To a stirred solution of *trans*-cinnamaldehyde (2.98 ml, 23.7 mmol) in CH_2Cl_2 (80 ml) at RT was added 4-methoxybenzylamine (3.40 ml, 26.0 mmol) dropwise. The reaction was heated to reflux for 1 hour to ensure complete imine formation then allowed to cool to RT. The solvent was evaporated *in vacuo* and the residue redissolved in MeOH (60 ml). The mixture was cooled to 0°C and sodium borohydride (2.70 g, 71.0 mmol) subsequently added portionwise over 45 minutes. The reaction was stirred at 0°C for 2 hours, then at RT for a further 18 hours. Aq. 1M

HCl (50 ml) was added dropwise to quench the reaction and the pH adjusted to 10 by the cautious addition of conc. NH_4OH. Water (100 ml) and CH_2Cl_2 (100 ml) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 80 ml), and the combined organic layers were washed with water (120 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow liquid. The crude amine was redissolved in EtOH (30 ml) and aq. 5M HCl (30 ml) was added, causing the HCl salt to precipitate immediately. The flask was cooled to 0°C for 1 hour to ensure maximum precipitation, before the salt was collected by suction filtration. Recrystallisation from EtOH gave the hydrochloride as white prisms. The free base was obtained by dissolving in aq. 3M NaOH (50 ml) and extracting with CH_2Cl_2 (3 × 50 ml). Drying ($MgSO_4$), filtering and evaporation of the solvent *in vacuo* afforded the title product as a colourless liquid (3.22 g, 49%); R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.41; ν_{max} (film) 1611, 1512, 1248 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 3.46 (2H, dd, *J* = 6.0, 1.2, $\mathbf{CH_2}$CH=CH), 3.82 (2H, s, NHC$\mathbf{H_2}$Ar), 3.84 (3H, s, OC$\mathbf{H_3}$), 6.36 (1H, dt, *J* = 15.6, 6.4, CH_2C**H**=CH), 6.58 (1H, d, *J* = 15.6, CH=C**H**Ph), 6.92 (2H, d-*pseudo*-t, *J* = 8.4, 2.0, 2 × Ar-**H**[*o*-OC$\mathbf{H_3}$]), 7.24-7.43 (7H, m, 7 × Ar**H**); δ_C (100 MHz, $CDCl_3$): 51.12, 52.74, 55.31, 113.86 (Ar-CH), 126.31 (Ar-CH), 127.40 (C=C), 128.40 (Ar-CH), 128.59 (Ar-CH), 129.48 (Ar-CH), 131.48 (C=C), 132.28 (Ar-C), 137.16 (Ar-C), 158.71 (Ar-C); FAB MS *m/z* 255 (MH^+, 100%); HRMS calc. for $C_{17}H_{20}NO$ 254.1544, found 254.1549

trans-2-{(4-Methoxybenzyl)[(*E*)-3-phenylprop-2-enyl]amino}cyclohexanol hydrochloride (138)

To a stirred suspension of **139**.HCl (4.62 g, 15.9 mmol) in 1,2-dichloroethane (45 ml) at RT was added *trans*-cinnamaldehyde (2.21 ml, 17.5 mmol) and triethylamine (2.66 ml, 19.1 mmol). Sodium triacetoxyborohydride (5.07 g, 23.9 mmol) was then added portionwise over 5 minutes and the reaction subsequently stirred for 16 hours at RT. Excess hydride was quenched by the cautious addition of aq. sat. $NaHCO_3$ (20 ml) and the resulting two-phase system was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The crude amine was treated with 5M HCl in propan-2-ol (40 ml) and the solvent removed to yield the hydrochloride salt. Recystallisation from propan-2-ol/diethyl

ether afforded the title product as white crystals (5.59 g, 90%); δ_H (400 MHz, $CDCl_3$): 1.22 (4H, br-*pseudo*-s, 4 × cyclo **CH**), 1.67-1.83 (2H, m, CH_2**CH**NBn), 1.90 (1H, m, CH_2**CH**OH), 2.16 (1H, m, CH_2**CH**OH), 2.48 (1H, m, CH_2**CH**NBn), 3.13 (1H, dd, *J* = 14.1, 8.4, NC**H**$_2$CH=CH), 3.34 (1H, d, *J* = 13.3, NC**H**$_2$Ar), 3.40-3.54 (2H, CH_2**CH**OH + NC**H**$_2$CH=CH), 3.79 (3H, s, O**CH**$_3$), 3.87 (1H, d, *J* = 13.3, NC**H**$_2$Ar), 6.10-6.22 (1H, m, CH_2**CH**=CH), 6.50 (1H, d, *J* = 16.1, CH=**CH**Ar), 6.88 (2H, d, *J* = 8.6, 2 × Ar-**H**[*o*-OCH_3]), 7.24 (2H, d, *J* = 8.6, 2 × Ar-**H**[*m*-OCH_3]), 7.30-7.40 (5H, m, 5 × Ar-**H**[cinnamyl]); δ_C (70 MHz, $CDCl_3$): 22.76, 24.27, 25.68, 33.34, 52.23, 53.08, 55.32, 65.26, 69.28, 113.97 (Ar-CH), 126.44 (Ar-CH), 127.56 (Ar-CH), 128.67 (Ar-CH), 130.13 (Ar-CH), 131.77 (Ar-C), 132.37 (Ar-CH), 137.11 (Ar-CH), 158.83 (Ar-CH)

***trans*-2-[(4-Methoxybenzyl)amino]cyclohexanol hydrochloride (139)**

4-Methoxybenzylamine (3.86 ml, 29.7 mmol) was added dropwise with stirring to cyclohexene oxide (3.00 ml, 29.7 mmol) at RT (no solvent). The mixture was stirred for 5 minutes, then lithium bistrifluoromethanesulfonimidate (1.70 g, 5.93 mmol) was added in small portions (warming was observed). The reaction was stirred vigorously at RT for 3 days, after which time CH_2Cl_2 (40 ml) and aq. sat. $NaHCO_3$ (15 ml) were added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 40 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. The crude amine was redissolved in EtOH (30 ml) and 5M HCl in propan-2-ol (30 ml) was added. The solvent was evaporated *in vacuo* and the resulting solid recrystallised from propan-1-ol to yield the hydrochloride salt as fine colourless prisms (5.35 g, 66%). The free base was prepared by treating the HCl salt with aq. 2M NaOH (40 ml) and extracting the resulting emulsion with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the title product as a colourless oil; R_f (10% MeOH: 89% CH_2Cl_2: 1% NH_4OH): 0.23; ν_{max} (film) 3294 and 3135 (O-H), 1613, 1517 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.95-1.07 (1H, m, cyclo **CH**), 1.16-1.32 (3H, m, 3 × cyclo **CH**), 1.68-1.76 (2H, *pseudo*-s, CH_2**CH**NH), 1.94-2.02 (1H, *pseudo*-s, CH_2**CH**OH), 2.11-2.18 (1H, *pseudo*-d, *J* = 12.8, CH_2**CH**OH), 2.26-2.34 (1H, **CH**NHBn), 3.20 (1H, td, *J* = 9.6, 3.6, **CH**OH), 3.62 (1H, dd, *J* = 12.8, 1.6, NHC**H**$_2$Ar), 3.80 (3H, s, O**CH**$_3$), 3.88 (1H, dd, *J* = 12.4,

1.6, $NHCH_2Ar$), 6.87 (2H, dd, J = 8.4, 1.2, 2 × Ar-**H**[*o*-OCH_3]), 7.26 (2H, d, J = 8.4, 2 × Ar-**H**[*m*-OCH_3]); δ_C (100 MHz, $CDCl_3$): 24.42, 25.05, 30.33, 33.56, 50.20, 55.26, 62.92, 73.53, 113.83 (Ar-CH), 129.36 (Ar-CH), 132.51 (Ar-C), 158.66 (Ar-C); FAB MS *m/z* 236 (MH^+, 50%)

Attempted preparation of *N*-(4-Methoxybenzyl)-*N*-[*trans*-2-(methylamino) cyclohexyl]-*N*-[(*E*)-3-phenylprop-2-enyl]amine (141)

To a stirred solution of **139** (1.24 g, 3.53 mmol) in anhydrous THF (30 ml) at 0°C under an atmosphere of nitrogen was added methanesulfonyl chloride (0.54 ml, 7.06 mmol) dropwise *via* a syringe. The mixture immediately became cloudy as triethylamine hydrochloride precipitated and the reaction was allowed to stir at 0°C for 2 hours. TLC analysis (50% EtOAc: 50% Hexanes) showed a prominent spot on the baseline by UV, suggesting formation of an aziridinium salt. Triethylamine (1.47 ml, 10.6 mmol) was added, after which the reaction was allowed to warm to RT. Methylamine (8.22 ml, 40% solution in water, 106 mmol) was subsequently added and the reaction stirred at RT for 1 hour. TLC analysis indicated the presence of a substantial amount of starting material and several polar compounds.

1-Methoxy-4-(4-methylpent-3-enyl)benzene (143)

Magnesium turnings (1.18 g, 48.5 mmol) (which had been previously washed with diethyl ether, dried overnight then ground in a pestle and mortar) and a few crystals of iodine were placed in an oven dried 250 ml round-bottomed flask and covered with anhydrous THF (5 ml) at RT. The flask was fitted with a pressure-equalising dropping funnel containing a solution of 4-methoxybenzyl chloride (6.00 ml, 44.1 mmol) in anhydrous THF (30 ml) and the system flushed with nitrogen. Addition of the halide solution was then commenced at such a rate as to maintain gentle reflux (20 minutes), after which the reaction was stirred for an additional 15 minutes to ensure complete consumption of the chloride. The dropping funnel was charged with a solution of 1-bromo-3-methyl-2-butene (5.69 ml, 44.1 mmol) in anhydrous THF (25 ml) and subsequently added dropwise to the Grignard reagent over 15 minutes. The reaction was stirred at RT for 1 hour, then quenched by the cautious addition of water (70 ml). Hexanes (100 ml) were added and the resulting two-phase system separated. The aqueous layer was extracted with hexanes (2 × 100

ml) and the combined organic layers were washed with water (150 ml), brine (100 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product as a colourless oil (8.05 g, 96%); R_f (50% EtOAc: 50% Hexanes): 0.59; δ_H (400 MHz, $CDCl_3$): 1.56 (3H, s, $C(\mathbf{CH_3})_2$), 1.68 (3H, s, $C(\mathbf{CH_3})_2$), 2.25 (2H, q, J = 7.6, $CH_2\mathbf{CH_2}CH$), 2.57 (2H, t, J = 7.6, $ArC\mathbf{H_2}CH_2$), 3.79 (3H, s, $OC\mathbf{H_3}$), 5.16 (1H, tt, J = 7.6, 1.6, $CH_2C\mathbf{H}=C(CH_3)_2$), 6.82 (2H, d, J = 8.4, 2 × Ar-**H**[*m*-OCH_3]), 7.10 (2H, d, J = 8.4, 2 × Ar-**H**[*o*-OCH_3]); δ_C (100 MHz, $CDCl_3$): 17.64, 22.65, 30.29, 35.19, 55.22, 113.60 (Ar-CH), 123.77 (C=CH), 129.28 (Ar-CH), 132.05 (Ar-C), 134.52 (C=CH), 157.63 (Ar-C); FAB MS *m/z* 190 (M^+, 90%)

2-Chloro-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (145)

To a stirred solution of alkene **143** (4.40 g, 23.1 mmol) in 5:1 acetone:water (70 ml) at RT was added trichloroisocyanuric acid (2.15 g, 9.25 mmol) in small portions over 5 minutes. Warming was observed during the addition and the reaction rapidly became cloudy. The system was stirred at RT for 3 hours after which time it was filtered under vacuum. The residual solid was washed with acetone (2 × 10 ml) and the filtrate concentrated *in vacuo* to leave an emulsion which was subsequently diluted with water (50 ml) and extracted with CH_2Cl_2 (3 × 70 ml). The combined organic layers were then washed with aq. 1M sodium metabisulfite (80 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (0-5% EtOAc: Hexanes: 1% Triethylamine) afforded the chlorohydrin as a mixture of regioisomers (1.63 g, 29%). 100% Sulfuric acid (0.72 ml, 13.4 mmol) was added to a mixture of 5 g of silica gel (which had been kept in an oven overnight then allowed to cool to RT) in CH_2Cl_2 (30 ml) and the resulting slurry stirred for 5 minutes at RT. A solution of chlorohydrin (1.63 g, 6.71 mmol) in CH_2Cl_2 (30 ml) was added dropwise over 10 minutes, causing a deep red colouration to develop. The reaction was allowed to stir at RT for 2 hours before quenching with propan-2-ol (10 ml). The silica gel was separated by suction filtration and washed with $CHCl_3$ (3 × 20 ml). Water (60 ml) was added to the filtrate and the layers separated. The aqueous layer was extracted with $CHCl_3$ (2 × 50 ml) and the combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (5% EtOAc: 95% Hexanes) afforded the title product as a yellow oil (1.17 g, 22% overall yield); R_f (50% EtOAc: 50% Hexanes): 0.67; δ_H (270

MHz, $CDCl_3$): 1.31 (3H, s, *gem*-CH_3), 1.34 (3H, s, *gem*-CH_3), 2.05-2.13 (2H, m, 3-CH_2), 2.69-2.94 (2H, m, 4-CH_2), 3.71 (3H, s, OCH_3), 4.12 (1H, dd, J = 9.0, 2.1, 2-CH), 6.63 (1H, dd, J = 8.4, 2.4, 6-ArH), 6.79 (1H, d, J = 2.1, 8-ArH), 6.90 (1H, d, J = 8.4, 5-ArH); δ_C (100 MHz, $CDCl_3$): 26.81, 27.23, 28.86, 29.73, 39.97, 55.23, 69.18, 111.64 (Ar-CH), 112.19 (Ar-CH), 125.89 (Ar-C), 129.68 (Ar-CH), 144.68 (Ar-C), 157.96 (Ar-C); FAB MS *m/z* 224 (M^+, 60%)

7-Methoxy-1,1-dimethyl-1,2-dihydronaphthalene (146) *via* KO^{t}Bu-promoted rearrangement of 141

To a stirred solution of **145** (0.25 g, 1.11 mmol) in anhydrous dimethylsulfoxide (5 ml) at RT was added potassium *tert*-butoxide (0.19 g, 1.67 mmol) in one portion. The reaction was heated at 60°C for 5 hours then allowed to cool to RT. The mixture was quenched by the cautious addition of water (10 ml). Pentane (30 ml) was added and the layers were separated. The organic layer was washed with water (2 × 20 ml), dried ($MgSO_4$), filtered and evaporated to afford the rearranged alkene (0.18 g); δ_H (270 MHz, $CDCl_3$): 1.24 (3H, s, *gem*-CH_3), 1.25 (3H, s, *gem*-CH_3), 2.19 (2H, dd, J = 4.2, 1.8, $CH_2C(CH_3)_2$), 3.80 (3H, s, OCH_3), 5.81 (1H, dt, J = 9.6, 5.0, $CH{=}CHCH_2$), 6.40 (1H, dd, J = 9.6, 1.7, ArCH=CH), 6.66 (1H, dd, J = 8.4, 2.5, 6-ArH), 6.87 (1H, d, J = 2.5, 8-ArH), 6.97 (1H, d, J = 8.4, 5-ArH)

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PUBLICATIONS AND PRESENTATIONS

Williams, I. A.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. Kappa opioid receptor antagonists in the 2-amino-1,1-dimethyl-7-hydroxytetralin series. *67th Annual Meeting of the College on Problems of Drug Dependence*, Orlando, Florida, United States, June **2005**

Grundt, P.; Williams, I. A.; Lewis, J. W.; Husbands, S. M. Identification of a new scaffold for opioid receptor antagonism based on the 2-amino-1,1-dimethyl-7-hydroxytetralin pharmacophore. *J. Med. Chem.* **2004**, *47*, 5069-5075.

Williams, I. A.; Lewis, J. W.; Husbands, S. M. Synthesis of 1,2-diamines by ring-opening of aziridines with non-activating *N*-substituents. Poster Presentation: *A Celebration of Organic Chemistry (SCI)*, University of Warwick, United Kingdom, September **2004**

Husbands, S. M.; Grundt, P.; Shefali; Williams, I.A.; Neal, A.; Lewis, J.W. New opioid antagonists based on the 2-amino-7-hydroxy-1,1-dimethyltetralin pharmacophore. *66th Annual Meeting of the College on Problems of Drug Dependence*, San Juan, Puerto Rico, June **2004**

Williams, I. A.; Grundt. P.; Lewis, J. W.; Husbands, S. M. New opioid antagonists based on the 2-amino-7-hydroxy-1,1-dimethyltetralin pharmacophore. Poster Presentation: *European Opioid Conference*, Visegrád, Hungary, April **2004**

Williams, I. A. Novel short-acting ligands for the kappa opioid receptor. Research Presentation: Department of Pharmacy and Pharmacology, University of Bath, United Kingdom, May **2003**

Identification of a New Scaffold for Opioid Receptor Antagonism Based on the 2-Amino-1,1-dimethyl-7-hydroxytetralin Pharmacophore

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The *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines are a unique class of opioid antagonists that have recently provided selective antagonists for μ-opioid receptors (MOR) and κ-opioid receptors (KOR). Molecular modeling indicated a strong structural similarity between the parent of this series and 2-amino-1,1-dimethyl-7-hydroxytetralin. In binding and in vitro functional assays, the aminotetralin derivatives displayed some overlap in SAR with that previously reported for the phenylpiperidine series, providing evidence for a common binding mode for the two series at opioid receptors. Introduction of a methoxy group in the 3-position increased potency at MOR and KOR receptors, suggesting that this aminotetralin skeleton can be utilized as a new scaffold for the design of selective opioid receptor antagonists.

Introduction

There has been considerable interest over many years in the development of selective ligands with which to study the function of opioid receptors.[1,2] Significant advances have been made with selective agonists and antagonists available for each of the three opioid receptors (μ, MOR; δ, DOR; κ, KOR).[1,3−5] Portoghese has developed both KOR- and DOR-selective antagonists by applying the message−address concept of Schwyzer to the opioid antagonist naltrexone (**1**, Chart 1), which itself is slightly MOR-selective.[6] The prototypic KOR-antagonist, developed in this way, is norBNI (**2**).[7] Portoghese has since shown that the large bimorphinan structure of **2** can be significantly simplified while retaining KOR selectivity and antagonist potency. This has ultimately led to the development of GNTI (**3**).[8]

The undoubted success of this approach means a large number of KOR and DOR antagonists have been synthesized on the basis of the oxymorphone framework. It is now desirable for the range of scaffolds to be increased because this could provide ligands with, for example, differing pharmacokinetic and pharmacodynamic properties or differing receptor subtype selectivity. In this regard, the provision of KOR antagonists that lack the extremely long duration of activity of **2** and **3** would be of particular value.

Carroll and co-workers have been successful in developing selective MOR and KOR antagonists based on an alternative to the oxymorphone framework, *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines, which produced a unique class of opioid antagonists, discovered by Zimmerman.[9−11] It was shown that modification of the N-substituent provided a means to control both the selectivity and potency of the ligands without introducing efficacy. By this approach, the selective MOR antagonist (**4a**)[10] and the highly selective KOR antagonist JDTic (**4b**)[11] were discovered. In these cases the phenylpiperidine unit acts as the message while the cinnamyl phenyl group and 7-hydroxyterahydroisoquinoline moieties provide the MOR and KOR address components, respectively.

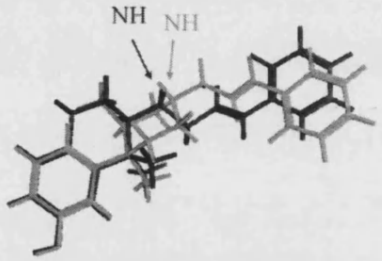

Figure 1. Overlay of **4a** (green) with **9k** (red).

We recognized the structural equivalence of the 14β-amino group in the morphinone series (**5**)[12] and the piperidine basic center in the phenylpiperidine series (**4**) in their spatial relationships to the respective phenolic binding centers. The 14β-alkylaminomorphinone series (**5a**), particularly those members with a side chain terminal aryl group, consistently provides potent opioid receptor antagonism with only low-level agonist activity. This SAR is characteristic also of the phenylpiperidine series (**4**). Though we investigated the 14β-cinnamylaminomorphinone (**5a**) and showed it to have potent noncompetitive MOR antagonist activity,[12] we were not immediately attracted to further investigation of the 14β-amino skeleton as a new message scaffold, particularly for introducing the address component for KOR selectivity because its synthesis from thebaine is multistep and very low yielding.[13] We considered the simpler but closely related aminobenzomorphan structure (**6**), but that too failed our criterion of ready accessibility.[14]

We therefore turned to an even simpler structure, 2-amino-1,1-dimethyl-7-hydroxytetralin (**7**). The 2-aminotetralin skeleton has previously been employed in the development of opioid analgesics.[15−17] A primary amino group was required for good in vivo analgesic activity with dezocine (**8**) the most well characterized example.[18] Because of their reduced analgesic potency, little atten-

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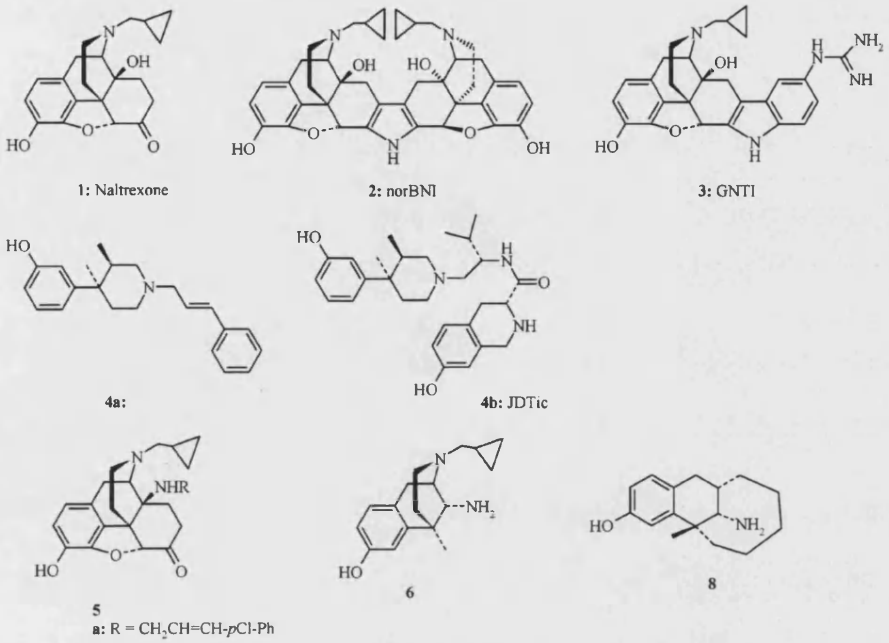
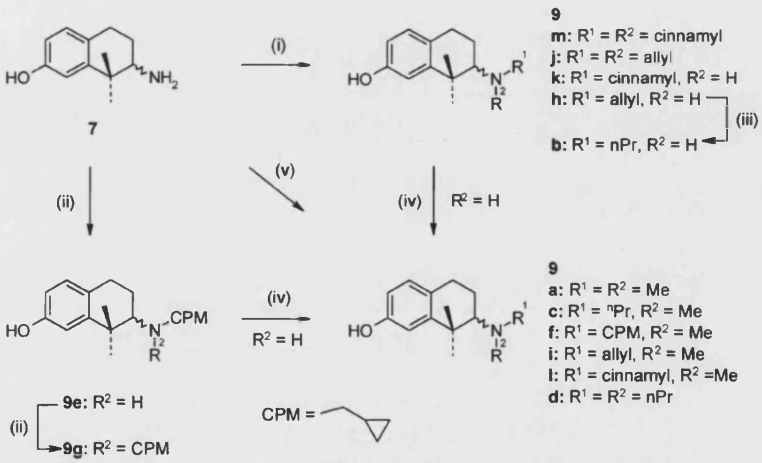
Chart 1



Scheme 1[a]



[a] Reagents and conditions: (i) RBr, $NaHCO_3$, DMF, 80 °C; (ii) cyclopropylcarbonyl chloride, then $LiAlH_4$; (iii) Pd, H_2; (iv) formaldehyde (1 equiv), $NaB(OAc)_3H$, CH_2Cl_2; (v) formaldehyde or propionaldehyde (2 equiv), $NaB(OAc)_3H$, CH_2Cl_2.

tion had previously been paid to secondary or tertiary amines.[16]

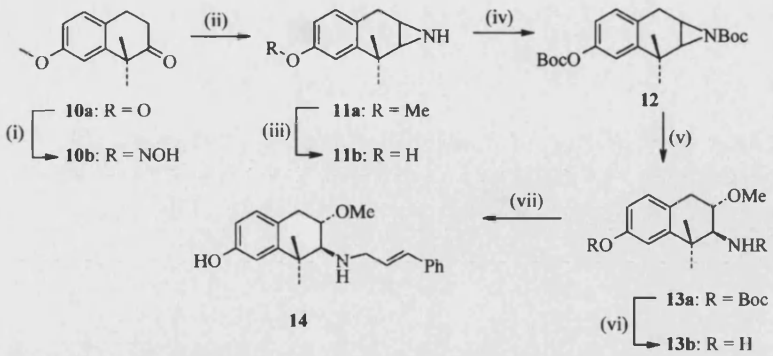
The validity of the choice of the aminotetralin (**7**) as a message scaffold for the design of selective antagonist ligands for MOR and KOR was confirmed by molecular modeling. Figure 1 shows the cinnamylphenylpiperidine derivative (**4a**) and the *R* enantiomer of the cinnamylaminotetralin derivative (**9k**) with the phenolic rings overlaid. In this orientation C_3, C_4, and the C_3 methyl group of the piperidine (**4a**) can overlay the reduced ring carbons of the tetralin while the latter's *gem*-dimethyl groups can overlay well with the C_4 methyl group and C_5 ring carbon of the piperidine. Importantly, this also allows the hydrogens of the protonated nitrogens to assume a common location, and the phenyl rings of the cinnamyl moieties are also in proximity to one another.

Our first targets were secondary and tertiary amine derivatives of (**7**) including those with cinnamyl groups. The secondary cinnamyl derivative (**9k**) had good MOR binding affinity and had moderate MOR and KOR antagonist potency. At the completion of this phase of the work, Roy et al. reported their work, based on the analgesic Dezocine, toward development of the aminotetralin pharmacophore for MOR agonist activity.[19] Their findings showed that a two-atom side chain α to the primary amino function gave optimal agonist potency. We resynthesized the published lead compound (**13b**) and a new cinnamyl derivative (**14**). The latter had high binding affinity particularly for MOR and high antagonist potency for MOR and KOR.

Chemistry

As depicted in Scheme 1, the synthesis of the substituted aminotetralins (**9a**−**m**) was accomplished by several methods. The tertiary amines (**9m**,**j**) and the secondary amines (**9k**,**h**) were prepared by direct alky-

Scheme 2[a]



[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, H_2O, MeOH; (ii) SMEAH, Bu(Me)NH, toluene; (iii) BBr_3, CH_2Cl_2; (iv) Boc_2O, DMAP, NEt_3, CH_2Cl_2; (v) MeOH, pyridinium *p*-toluenesulfonate; (vi) TFA, CH_2Cl_2; (vii) PhCH=CHCHO, CH_2Cl_2, then $NaBH_4$, MeOH.

Table 1. Binding Affinities to Opioid Receptors[a]

			$K_i \pm$ SEM (nM)		
compd	R^1	R^2	[^{3}H]DAMGO μ	[^{3}H]Cl-DPDPE δ	[^{3}H]U69,593 κ
9a	Me	Me	114 ± 31.7	4010 ± 399	333 ± 65.8
9b	^{n}Pr	H	491 ± 48.0	>10000	251 ± 55.0
9c	^{n}Pr	Me	85.0 ± 14.7	2090 ± 22.8	184 ± 29.4
9d	^{n}Pr	^{n}Pr	482 ± 61.1	2720 ± 780	552 ± 42.5
9e	CPM	H	312 ± 45.0	3830 ± 159	232 ± 4.80
9f	CPM	Me	104 ± 24.5	601 ± 84.0	146 ± 13.7
9g	CPM	CPM	422 ± 46.7	5770 ± 591	1830 ± 517
9h	allyl	H	202 ± 0.92	5830 ± 682	63.7 ± 6.60
9i	allyl	Me	1080 ± 142	2220 ± 484	263 ± 5.10
9j	allyl	allyl	105 ± 0.89	672 ± 127	55.8 ± 18.6
9k	cinnamyl	H	10.7 ± 2.73	472 ± 108	82.3 ± 18.0
9l	cinnamyl	Me	39.7 ± 11.7	591 ± 27.3	207 ± 29.6
9m	cinnamyl	cinnamyl	268 ± 53.4	>10000	1250 ± 143
13b			17.5 ± 5.90	2430 ± 422	149 ± 2.15
14			1.63 ± 0.58	22.4 ± 6.70	7.50 ± 0.84
naltrexone			0.2 ± 0.0	10.8 ± 3.0	0.4 ± 0.1
naltrindole			6.3 ± 2.3	0.2±0.05	10.1 ± 0.65
norBNI			21.0 ± 5.0	5.7 ± 0.9	0.2 ± 0.05

[a] Data provided through NIDA (OTDP).

lation of the known 7-amino-8,8-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**7**)[14] using the appropriate alkyl bromide. The most reliable method for synthesis of the monopropyl analogue (**9b**) proved to be hydrogenation of the allyl group of **9h**. The cyclopropylmethylamines (**9e**,**g**) were prepared by sequences of acylation with cyclopropylcarbonyl chloride and subsequent reduction with $LiAlH_4$. The methylamines (**9a**,**c**,**f**,**i**,**l**) and the dipropylamine (**9d**) were synthesized by reductive amination using sodium triacetoxyborohydride as the reducing agent.

The synthesis of **13b** has been reported previously (Scheme 2).[19] While the use of $LiAlH_4$ in the presence of DEA was reported to give good yields (60%) of aziridine (**11a**) from the oxime (**10b**), we were unable to carry out the reaction in a reproducible manner. An alternative method utilizing RedAl with *N*-methylbutylamine gave **11a** in lower, but reproducible, 40% yield (Scheme 2). Ring opening with MeOH under acid catalysis followed by removal of the Boc protecting group gave **13b**. The cinnamyl group was introduced by reaction with cinnamaldehyde and subsequent reduction with $NaBH_4$ (**14**).

Results and Discussion

The ligands were evaluated in competition binding assays in Chinese hamster ovary (CHO) cells transfected with cloned human opioid receptors (Table 1).[20] The displaced radioligands were [^{3}H]DAMGO (MOR), [^{3}H]Cl-DPDPE (DOR), and [^{3}H]U69,593 (KOR). The simplest tertiary amino derivative (**9a**) had modest affinity for MOR and KOR but very low affinity for DOR. Replacement of one of the methyl groups of **9a** by *n*-propyl, allyl, or cyclopropylmethyl (piperidine N-substituents that give antagonist activity in the epoxymorphinan, morphinan, and benzomorphan series) had variable effects on opioid receptor affinity. The *n*-propyl analogue (**9c**) had affinity similar to that of **9a** for all opioid receptors. The allyl analogue (**9i**) had KOR and DOR affinity similar to that of **9a** but an order of magnitude lower affinity for MOR. The cyclopropylmethyl (CPM) derivative (**9f**) had MOR affinity similar to that of **9a** but somewhat higher KOR affinity and substantially higher DOR affinity. The effect of replacing the *N*-methyl group in **9c** by a second propyl group (**9d**) was to reduce KOR and MOR affinity. Similar replacement of the *N*-methyl group in **9f** by a second CPM group (**9g**) had an equivalent but more pronounced effect having 4-fold lower MOR affinity and an order of magnitude lower KOR and DOR affinity. Surprisingly the bis-allylamine (**9j**) had substantially higher affinity than the monoallyl tertiary amine (**9i**) for all opioid receptor types but particularly for MOR.

Table 2. Antagonist Potencies in [^{35}S]GTPγS Assays Performed in Cloned Human Opioid Receptors[a]

compd	R^1	R^2	K_e ± SEM (nM) vs DAMGO μ	vs DPDPE δ	vs U69,593 κ
9k	cinnamyl	H	67.7 ± 7.59	NT	42.7 ± 2.75
13b			agonist[b]	NT	49.3 ± 4.3
14			2.62 ± 0.40	26.3 ± 3.90	2.12 ± 0.11
naltrexone			0.59 ± 0.04	5.44 ± 0.75	1.86 ± 0.16
naltrindole			4.26 ± 0.33	0.11 ± 0.005	4.95 ± 0.32
norBNI			18.9 ± 1.80	4.42 ± 0.38	0.039 ± 0.004

[a] Data provided by NIDA (OTDP). [b] Agonist IC_{50} = 234 ± 55 nM, 31.6% stimulation relative to the standard μ agonist DAMGO.

The propyl and CPM secondary amines (**9b,e**) had lower affinity than the equivalent *N*-methyl tertiary amines, but the secondary allylamine (**9h**) had substantially higher affinity for MOR than the tertiary amine (**9i**). The secondary allylamine (**9h**) and the bisallylamine (**9j**) had higher KOR affinity than any of the other new ligands. The tertiary cinnamylamine (**9l**) had higher MOR affinity than any of the other tertiary amines, together with modest selectivity for MOR over KOR and substantial selectivity for MOR over DOR. The bis-cinnamylamine (**9m**) had lower affinity than **9l**, but the secondary cinnamylamine (**9k**) had higher affinity than **9l**, and its MOR affinity (K_i = 10.6 nM) was the highest recorded for any opioid receptor by ligands of structure **9**. It had 8-fold selectivity for MOR over KOR and 45-fold selectivity for MOR over DOR. This is reminiscent of the findings of Zimmerman who showed that a phenyl ring separated by a three-atom chain from their phenylpiperidine scaffold was optimal for MOR affinity and antagonist activity.[9] In the present series, in no case was significant affinity seen for the DOR, with the highest affinity (K_i = 471 nM) displayed by **9k**.

For ligands having K_i values of 200 nM or better in the binding assays, opioid agonist and antagonist activity was determined using the [^{35}S]GTPγS assay in cloned human opioid receptors transfected into CHO cells.[20] Only one of the new ligands of type **9**, the secondary cinnamylamine (**9k**), had significant activity in this assay (Table 2) with no other ligand displaying a K_e, at any receptor, better than 500 nM. **9k** was a moderately potent antagonist of MOR and KOR with no selectivity. Nevertheless, it was of great significance that **9k** was an antagonist in the in vitro functional assays, thus further confirming the relationship of this series to the phenylpiperidines. As was to be expected there was little similarity in the effect of N-substitution between the aminotetralins (**9**) and the basic N-atom in the epoxymorphinan, morphinan, and benzomorphan series.[21] In these series arylalkyl substitution, particularly phenethyl, enhanced agonist (antinociceptive) activity. Though antinociceptive potency was substantially lower for cinnamyl, phenylpropyl, and phenylbutyl substitution, there was no evidence of morphine antagonist activity.

The *trans*-3-methoxy-substituted analogue **14** had much higher affinity for all opioid receptor types than the lead compound **9k** from the aminotetralin series (Table 1). MOR affinity for **14** was 6.5-fold higher, KOR affinity 11-fold higher, and DOR affinity 21-fold higher than for **9k**. Compared with the previously reported primary amine (**13b**),[19] the cinnamylamino derivative **14** also had much higher affinity, 11-fold for MOR, 20-fold for KOR, and 108-fold for DOR. In [^{35}S]GTPγS assays **14** showed potent MOR and KOR antagonist activity, and in each case potency was ~20-fold greater than for **9k**. Interestingly, though the primary amine was reported to have potent antinociceptive activity,[19] in the GTPγS assay it was a low potency, low efficacy MOR partial agonist and a KOR antagonist.

Conclusions

In conclusion, it is clear that the 2-amino-1,1-dimethyl-7-hydroxytetralin skeleton, particularly when incorporating an appropriate functional group (e.g., OMe) in the 3-position and trans to the C_2 amine, offers an alternative scaffold for the design of receptor selective opioid ligands. The ligands produced were comparable to their *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine analogues in opioid binding affinity and antagonist potency. We are currently investigating the use of this skeleton in the preparation of KOR selective antagonists.

Experimental Section

Column chromatography was performed under gravity over silica gel 60 (35−70 μm) purchased from Merck. Preparative TLC was performed on plates made with Kieselgel 60 $PF_{254-366}$, obtained from Merck. The thickness of the silica layer was approximately 1 mm. Analytical TLC was performed using aluminum-backed plates coated with Kieselgel 60 F_{254}, from Merck. The chromatograms were visualized using either UV light (UVGL-58, short wavelength), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High- and low-resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzyl alcohol. High- and low-resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. ^{1}H NMR and ^{13}C NMR spectra were recorded using JEOL EX 400 (operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C) or JEOL GX270 (operating at 270 MHz for ^{1}H and 68 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are measured in ppm relative to TMS. Coupling constants (J) are expressed in Hz. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Anhydrous THF, DMF, DCM, and MeOH were purchased from Aldrich. All other solvents used were GPR grade, purchased from Merck or Fisher Scientific. Chemicals were purchased from Aldrich, Fluka, Lancaster, and Acros chemical companies.

General Methods. Procedure A. To a solution of the appropriate amine (1.0 mmol) in CH_2Cl_2 (10 mL) was added formaldehyde (75 μL, 1 mmol, 37 wt %) followed by a spatula tip of $MgSO_4$ to remove excess water. This mixture was then treated with solid sodium triacetoxyborohydride (0.29 g, 1.4 mmol) and stirred at room temperature overnight under an atmosphere of nitrogen. The mixture was quenched by the addition of saturated aqueous Na_2CO_3 solution, and the product was extracted into CH_2Cl_2. The combined extracts were dried ($MgSO_4$) to give the crude free base that was purified by thin-layer chromatography or flash chromatography followed by crystallization from methanolic HCl/Et_2O.

Procedure B. A suspension of 0.19 g (1.0 mmol) of 2-amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (**7**), sodium bicarbonate (0.21 g, 2.5 mmol), and the appropriate alkyl bromide (1.2 mmol) in 10 mL of DMF was heated at 80 °C for 16 h. Upon completion of the reaction, the volatiles were removed in vacuo and the residue was purified by flash chromatography or thin-layer chromatography followed by cystallization from methanolic HCl/Et_2O.

2-(Dimethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9a). 9a was prepared from **7** with procedure A, using double the amount of formaldehyde and sodium triacetoxyborohydride. Yield: 59%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.34. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.36 (s, 3H), 1.68 (m, 1H), 1.96 (m, 1H), 2.36 (s, 6H), 2.50 (dd, J 11.9, 2.9, 1H), 2.71−2.89 (m, 2H), 6.37 (br, 1H), 6.60 (dd, J 8.2, 2.7, 1H), 6.81 (d, J 2.3, 1H), 6.88 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 18.62, 26.67, 29.21, 30.56, 40.83, 44.55, 69.61, 113.43, 113.97, 127.16, 129.73, 148.27, 154.07. EIMS (CI) *m/z* (%): 219 (100). HRMS ($C_{14}H_{21}NO$): calcd 219.1623, found 219.1617. Anal. ($C_{14}H_{21}NO$·HCl) C, H, N.

1,1-Dimethyl-2-propylamino-1,2,3,4-tetrahydronaphthalen-7-ol (9b). A suspension of 0.25 g (1.08 mmol) of **9h** and 0.11 g of Pd/C (10%) in EtOH (50 mL) was stirred in a hydrogen atmosphere for 24 h. The catalyst was removed by filtration over Celite, and the crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 100:10:1) to give 0.18 g (77%) of **9b** as a solid. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.40. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J 7.4, 3H), 1.19 (s, 3H), 1.32 (s, 3H), 1.54 (sext, J 7.4, 2H), 1.74 (m, 1H), 2.01 (m, 1H), 2.50−2.87 (m, 5H), 4.34 (br, 2H), 6.55 (d, J 8.2, 2.3, 1H), 6.77 (d, J 2.3, 1H), 6.85 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.30 23.42, 24.19, 26.02, 28.12, 29.47, 39.00, 50.76, 63.76, 113.77, 113.92, 126.55, 129.83, 146.63, 154.73. EIMS *m/z* (%): 234 (7), 233 (37), 148 (100). HRMS ($C_{15}H_{23}NO$): calcd 233.1780, found 233.1772. Anal. ($C_{15}H_{23}NO$·HCl) C, H, N.

1,1-Dimethyl-2-(propylmethylamino)-1,2,3,4-tetrahydronaphthalen-7-ol (9c). 9c was prepared from **9b** with procedure A. Yield: 46%. Mp (hydrochloride): 192 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.36. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J 7.4, 3H), 1.18 (s, 3H), 1.35 (s, 3H), 1.53 (m, 1H), 1.69 (m, 1H), 1.89 (m, 1H), 2.29 (s, 3H), 2.35 (m, 1H), 2.49−2.56 (m, 2H), 2.68−2.84 (m, 3H), 4.72 (br, 1H), 6.57 (dd, J 8.2, 2.7, 1H), 6.79 (d, J 2.7, 1H), 6.86 (d. J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.25, 19.68, 21.60, 26.78, 28.97, 30.91, 40.16, 40.79, 60.00, 68.63, 113.26, 114.04, 127.47, 129.77, 148.72, 153.76. EIMS *m/z* (%): 247 (59), 148 (100), 42 (99). HRMS ($C_{16}H_{25}NO$): calcd 247.1936, found 247.1934. Anal. ($C_{16}H_{25}NO$·HCl·0.5H_2O·0.25CH_3OH) C, H, N.

2-(Dipropylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9d). 9d was prepared from **7** with procedure A, using double the amount of propionaldehyde and sodium triacetoxyborohydride. Yield: 0.18 g (45%). Mp (hydrochloride): 119 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.35. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J 7.4, 6H), 1.15 (s, 3H), 1.32 (s, 3H), 1.36−1.54 (m, 4H), 1.75 (m, 1H), 1.86 (m, 1H), 2.40 (t, J 7.4, 4H), 2.54 (dd, J 12.3, 2.5, 1H), 2.68−2.86 (m, 2H), 4.3 (br, 1H), 6.57 (dd, J 8.2, 2.7, 1H), 6.81 (d, J 2.7, 1H), 6.87 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.04, 19.81, 21.87, 26.59, 28.59, 31.01, 40.32, 54.70, 66.57, 112.79, 113.68, 127.31, 129.51, 148.82, 153.41. EIMS *m/z* (%): 275 (39), 148 (52), 43 (100). HRMS ($C_{18}H_{29}NO$): calcd 275.2249, found 275.2245. Anal. ($C_{18}H_{29}NO$·HCl·0.25H_2O) C, H, N.

2-(Cyclopropylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9e). A solution of 7-amino-8,8-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**7**) (0.19 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was treated with cyclopropylcarbonyl chloride (2.2 mmol) followed by triethylamine (0.5 mL). The resulting mixture was stirred at room temperature overnight. After this time the reaction mixture was washed with water and brine and the solvent was evaporated. The residue was redissolved in anhydrous THF (10 mL), and $LiAlH_4$ (0.1 g) was added carefully. After 3 h, excess $LiAlH_4$ was destroyed with Glauber's salt and the reaction mixture was filtered. The crude product was purified by flash chromatography followed by cystallization from methanolic HCl/Et_2O. Yield: 69%. Mp (hydrochloride): >200 °C. Signs of decomposition: >175 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.37. ^1H NMR (400 MHz, $CDCl_3$): δ 0.14 (m, 2H), 0.48 (m, 2H), 1.04 (m, 1H), 1.21 (s, 3H), 1.34 (s, 3H), 1.73 (m, 1H), 2.01 (m, 1H), 2.42 (dd, J 12.1, 7.4, 1H), 2.59 (dd, J 10.2, 2.7, 1H), 2.63−2.82 (m, 3H), 3.91 (br, 2H), 6.55 (dd, J 8.2, 2.7, 1H), 6.78 (d, J 2.7, 1H), 6.84 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 3.42, 3.89, 11.29, 23.85, 25.65, 27.72, 29.14, 38.68, 53.63, 63.20, 113.34, 113.52, 126.36, 129.52, 146.37, 154.23. EIMS *m/z* (%): 245 (62), 148 (100). HRMS ($C_{16}H_{23}NO$): calcd 245.1780, found 245.1774. Anal. ($C_{16}H_{23}NO$·HCl·0.25CH_3OH) C, H, N.

2-(Cyclopropylmethylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9f). 9f was prepared from **9e** with procedure A. Yield: 57%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.37. ^1H NMR (400 MHz, $CDCl_3$): δ 0.13 (m, 2H), 0.51 (m, 2H), 0.95 (m, 1H), 1.24 (s, 3H), 1.39 (s, 3H), 1.71 (m, 1H), 1.95 m, 1H), 2.42 (dd, J 12.9, 6.6, 1H), 2.42 (s, 3H), 2.59 (dd, J 12.8, 5.9, 1H), 2.61−0.88 (m, 3H), 5.91 (br, 1H), 6.62 (dd, J 8.2, 2.7, 1H), 6.85 (d, J 2.7, 1H), 6.89 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 3.42, 4.81, 9.73, 19.47, 26.46, 28.69, 30.51, 39.80, 40.62, 62.94, 67.45, 113.15, 113.85, 126.90, 129.41, 148.20, 153.58. EIMS *m/z* (%): 260 (10), 259 (51), 204 (34), 148 (89), 55 (100). HRMS ($C_{17}H_{25}NO$): calcd 259.1936, found 259.1921. Anal. ($C_{17}H_{25}NO$·HCl·0.25$CHCl_3$) C, H, N.

2-(Bis-cyclopropylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9g). 9g was prepared from **9e**. The sequence for the formation of **9e** was repeated. Yield: 64%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.60. ^1H NMR (400 MHz, $CDCl_3$): δ 0.14 (m, 4H), 0.43 (m, 2H), 0.57 (m, 2H), 0.94 (m, 2H), 1.23 (s, 3H), 1.42 (s, 3H), 1.76 m, 1H), 1.93 (m, 1H), 2.42 (m, 2H), 2.69−2.93 (m, 4H), 5.11 (br, 1H), 6.62 (dd, J 8.2, 2.7, 1H), 6.85 (d, J 2.7, 1H), 6.90 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 2.47, 5.74, 10.11, 20.23, 26.55, 28.71, 30.95, 40.57, 56.89, 65.63, 112.87, 113.80, 127.28, 129.50, 148.71, 153.33. EIMS *m/z* (%): 299 (17), 244 (10), 55 (100). HRMS ($C_{20}H_{29}NO$): calcd 299.2249, found 299.2237. Anal. ($C_{20}H_{29}NO$·HCl·0.25$CHCl_3$·0.25H_2O) C, H, N.

2-Diallylamino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9j) and 2-(Allylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9h). 9j and **9h** were prepared from **7** and allyl bromide with procedure B.

Fraction 1 Containing 9j. Yield: 15%. Mp (hydrochloride): 99 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.60. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.33 (s, 3H), 1.73 (m, 1H), 1.84 (m, 1H), 2.69−2.84 (m, 3H), 2.99 (dd, J 14.6, 8.0, 2H), 3.26 (m, 2H), 5.08 (dd, J 10.2, 1.6, 2H), 5.16 (m, 1.2, 2H), 5.86 (m, 2H), 6.56 (dd, J 8.2, 2.3, 1H), 6.80 (d, J 2.7, 1H), 6.88 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.23, 26.27, 28.71, 30.63, 40.45, 55.12, 64.32, 112.85, 113.71, 116.20, 127.25, 129.51, 137.06, 148.41, 153.33. EIMS *m/z* (%): 271 (23), 122 (42), 41 (100). HRMS ($C_{18}H_{25}NO$): calcd 271.1936, found 271.1933. Anal. ($C_{18}H_{25}NO$·HCl·0.75H_2O) C, H, N.

Fraction 2 Containing 9h. Yield: 41%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.36. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.32 (s, 3H), 1.72 (m, 1H), 2.02 (m, 1H), 2.62 (dd, 10.5, 2.7, 1H), 2.67−2.82 (m, 2H), 3.24 (dd, J 13.7, 7.0, 1H), 3.51 (dd, J 13.7, 5.5, 1H), 4.34 (br, 2H), 5.11 (d, J 10.2, 1H), 5.20 (dd, J 17.2, 1.6, 1H), 5.92 (m, 1H), 6.55 (dd, J 8.2, 2.3, 1H), 6.76 (d, J 2.7, 1H), 6.85 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.87, 26.10, 27.98, 29.58, 39.01, 51.10, 62.67, 113.89, 113.97, 117.47, 126.73, 129.95, 136.45, 146.61, 154.53. EIMS *m/z* (%): 232 (3), 231 (17), 159 (27), 148 (94), 41 (100). HRMS ($C_{15}H_{21}NO$): calcd 231.1623, found 231.161. Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

2-(Allylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9i). 9i was prepared from **9h** with procedure A. Yield: 71%. Mp (hydrochloride): >200 °C. Signs of decomposition: >150 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.39. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.36 (s, 3H), 1.73 (m, 1H), 1.90 (m, 1H), 2.33 (s, 3H), 2.62 (dd, J 12.1, 2.7, 1H), 2.72−2.88 (m, 2H), 3.02 (dd, J 14.1, 7.0, 1H), 3.29 (dd, J 14.1, 5.5, 1H), 5.10 (dd, J 10.9, 0.8, 1H), 5.19 (dd, J 17.0, 1.8, 1H), 5.35 (br, 1H), 5.85 (m, 1H), 6.59 (dd, J 8.2, 2.7, 1H), 6.82 (d, J 2.3, 1H), 6.89 (d, J 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.37, 26.37, 28.67, 30.43, 40.29, 40.61, 60.18, 67.30, 113.01, 113.75, 116.32, 127.15, 129.47, 136.84, 148.23, 153.37.

EIMS *m/z* (%): 245 (35), 41 (100). HRMS ($C_{16}H_{23}NO$): calcd 245.1780, found 245.1775. Anal. ($C_{16}H_{23}NO \cdot HCl \cdot H_2O$) C, H, N.

2-{Bis-[(*E*)-3-phenylprop-2-enyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9m) and 1,1-Dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydronaphthalen-7-ol (9k). 9m and **9k** were prepared from **7** and cinnamyl bromide with procedure B.

Fraction 1 Containing 9m. Yield: 7%. Mp (hydrochloride): 148 °C (dec). R_f (EtOAc): 0.89. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.39 (s, 3H), 1.79 (m, 1H), 1.92 (m, 1H), 2.71−2.86 (m, 3H), 3.23 (m, 2H), 3.49 (m, 2H), 4.08 (br, 1H), 6.29 (ddd, *J* 16.0, 8.2, 4.7, 2H), 6.53 (d, *J* 14.8, 2H), 6.54 (dd, *J* 8.2, 2.3, 1H), 6.79 (d, *J* 2.7, 1H), 6.86 (d, *J* 8.2, 1H), 7.20 (m, 2H), 7.29 (m, 4H), 7.37 (d, *J* 7.8, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.45, 26.47, 28.86, 30.68, 40.57, 54.67, 64.68, 112.89, 113.67, 126.12, 127.09, 127.15, 128.43, 128.96, 129.53, 131.40, 137.22, 148.21, 153.39. EIMS *m/z* (%): 423 (4), 307 (66), 35 (100). HRMS ($C_{30}H_{33}NO$): calcd 423.2562, found 423.2573. Anal. ($C_{30}H_{33}NO \cdot HCl$) C, H, N.

Fraction 2 Containing 9k. Yield: 60%. Mp (hydrochloride): >200 °C. Signs of decomposition: >175 °C. R_f (EtOAc): 0.70. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.34 (s, 3H), 1.74 (m, 1H), 2.08 (m, 1H), 2.61−2.82 (m, 3H), 3.38 (ddd, *J* 13.7, 7.0, 0.8, 1H), 3.42 (br, 1H), 3.62 (ddd, *J* 13.7, 5.9, 1.6, 1H), 6.32 (m, 1H), 6.53−6.59 (m, 2H), 6.78 (d, *J* 2.7, 1H), 6.88 (d, *J* 8.5, 1H), 7.19−7.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.10, 26.16, 28.07, 29.68, 39.12, 50.73, 62.79, 113.98, 114.10, 126.61, 126.89, 127.75, 128.42, 128.82, 130.03, 132.29, 137.19, 146.78, 154.53. EIMS *m/z* (%): 307 (7), 173 (19), 148 (17), 117 (29), 82 (100). HRMS ($C_{21}H_{25}NO$): calcd 307.1936, found 307.1927. Anal. ($C_{21}H_{25}NO \cdot HCl$) C, H, N.

1,1-Dimethyl-2-{methyl-[(*E*)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydro-naphthalen-7-ol (9l). 9l was prepared from **9k** with procedure A. Yield 45%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.85. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.40 (s, 3H), 1.76 (m, 1H), 1.93 (m, 1H), 2.38 (s, 3H), 2.63−2.89 (m, 3H), 3.19 dd, 4.1, 7.4, 1H), 3.44 (dd, *J* 14.1, 5.1, 1H), 6.32 (ddd, *J* 15.6, 7.0, 5.5, 1H), 6.52 (d, *J* 15.6, 1H), 6.59 (dd, *J* 8.2, 2.7, 1H), 6.83 (d, *J* 2.7, 1H), 6.89 (d, *J* 8.2, 1H), 7.24 (m, 1H), 7.32 (t, *J* 7.6, 2H), 7.39 (d, *J* 8.2, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.80, 26.78, 29.03, 30.79, 40.80, 41.02, 59.82, 67.70, 113.17, 113.92, 126.44, 127.42, 127.49, 28.73, 129.15, 129.80, 131.58, 137.50, 148.53, 153.73. EIMS *m/z* (%): 321 (1), 188 (45), 173 (69), 162 (100). HRMS ($C_{22}H_{28}ClNO$): calcd 321.2093, found 321.2090. Anal. ($C_{22}H_{28}ClNO \cdot 0.5H_2O$) C, H, N.

7-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2-one Oxime (10b). To a vigorously stirred solution of hydroxylamine hydrochloride (3.79 g, 54.5 mmol) and sodium acetate (4.47 g, 54.5 mmol) in H_2O (30 mL) was added a solution of **10a** (3.71 g, 18.2 mmol) in MeOH (30 mL). Stirring was continued for 10 min at 60 °C and then for a further 15 h at room temperature. After this time the solid oxime was collected by suction filtration and washed with ice-cold MeOH (2 × 5 mL), leaving the title product as a white solid (2.13 g, 54%). R_f (50% EtOAc/50% hexane): 0.59. Mp 140−142 °C. IR, ν_{max} (KBr): 1628 (C=N). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.50 (s, 6H), 2.79−2.92 (m, 4H), 3.81 (s, 3H), 6.71 (dd, *J* 8.4, 2.6, 1H), 6.94 (d, *J* 2.6, 1H), 7.06 (d, *J* 8.4, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.23, 27.05, 27.99, 41.20, 55.41, 111.13, 111.51, 128.62, 129.22, 145.07, 158.61, 165.10. EIMS *m/z* (%): 219 (65).

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphtho[2,3]-azirene (11a). To a stirred solution of **10b** (1.50 g, 6.85 mmol) and *N*-methylbutylamine (0.1 mL) in toluene at 0 °C was added sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in toluene, 10.7 mL, 34.2 mmol) dropwise over 10 min. The mixture was heated to reflux for 15 h and then allowed to cool to room temperature. The reaction was quenched by the dropwise addition of 2 M HCl (50 mL), and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 70 mL) and then basified to pH 10 with 10 M NH_4OH. The free base was extracted into CH_2Cl_2 (3 × 70 mL), and the combined organic layers were washed with H_2O (2 × 150 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave a brown oil. Column chromatography (5% MeOH/94% DCM/1% NH_4OH) afforded the title product as a yellow oil (0.48 g, 35%). R_f (10% MeOH/89% DCM:/1% NH_4OH): 0.51. IR, ν_{max} (film): 3300 (N−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.51 (s, 3H), 2.12 (d, *J* 6.2, 1H), 2.47 (d, *J* 5.7, 1H), 3.14 (s, 2H), 3.78 (s, 3H), 6.69 (dd, *J* 8.2, 2.5, 1H), 6.85 (d, *J* 2.5, 1H), 6.96 (d, *J* 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 26.90, 29.36, 29.49, 29.54, 35.94, 41.31, 55.09, 111.38, 111.81, 122.58, 130.43, 142.83, 158.64. EIMS *m/z* (%): 203 (60).

1,1-Dimethyl-1,2,3,4-tetrahydronaphtho[2,3]aziren-7-ol (11b). A solution of **11a** (0.47 g, 2.31 mmol) in DCM (10 mL) was treated with boron tribromide (1 M solution in DCM, 4.6 mL, 4.60 mmol) at −78 °C. After 15 h the reaction was quenched by dropwise addition of MeOH (5 mL). The solvent was evaporated, and the residue was redissolved in MeOH (10 mL). After the mixture was stirred for 15 min, the solvent was again evaporated and the residue made basic (pH 10) with 10 M NH_4OH. H_2O (10 mL) was added followed by extraction with $CHCl_3$/EtOH (3:1, 3 × 15 mL). The combined organics were washed (H_2O), dried ($MgSO_4$), and evaporated. Column chromatography (4% MeOH/95% DCM/1% NH_4OH) afforded the title product as a brown foam (0.32 g, 73%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.39. IR, ν_{max} (film): 3284 (O−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.45 (s, 3H), 2.16 (d, *J* 6.2, 1H), 2.51 (d, *J* 6.0, 1H), 3.12 (d, *J* 7.9, 2H), 5.25 (s, 1H), 6.55 (dd, *J* 8.2, 2.5, 1H), 6.71 (d, *J* 2.5, 1H), 6.82 (d, *J* 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.18, 28.87, 29.59, 30.63, 35.84, 42.09, 113.14, 114.68, 119.93, 130.90, 141.82, 156.92. EIMS *m/z* (%): 189 (20).

***tert*-Butyl 7-[(*tert*-Butoxycarbonyl)oxy]-1,1-dimethyl-1,2,3,4-tetrahydronaphtho[2,3]azirene-1′-carboxylate (12).** To a stirred solution of **11b** (0.38 g, 2.01 mmol), 4,4-(dimethylamino)pyridine (0.07 g, 0.57 mmol), and triethylamine (0.56 mL, 4.02 mmol) in DCM (8 mL) was added di-*tert*-butyl dicarbonate (0.88 g, 4.02 mmol). The mixture was allowed to stir at room temperature for 5 h, after which the solvent was evaporated in vacuo. The residue was partitioned between EtOAc (30 mL) and 1 M HCl (30 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Purification by column chromatography (20% EtOAc/80% hexane) afforded the title product as a colorless oil (0.51 g, 65%). R_f (50% EtOAc/50% hexane) 0.70. IR, ν_{max} (film): 1757, 1716 (2 × C=O). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.38 (s, 9H), 1.44 (s, 3H), 1.52 (s, 9H), 2.52 (d, *J* 6.7, 1H), 2.94 (m, 1H), 3.02 (m, 1H), 3.27 (d, *J* 15.6, 1H), 6.92 (dd, *J* 8.2, 2.5, 1H), 6.98 (d, *J* 8.2, 1H), 7.05 (d, *J* 2.5, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.96, 22.84, 24.06, 24.22, 25.25, 25.58, 27.92, 31.88, 33.12, 43.81, 77.00, 79.50, 114.70, 115.54, 124.57, 126.48, 139.61, 146.42. FAB MS *m/z* (%): 390 (40).

2-[(*tert*-Butoxycarbonyl)amino]-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-yl *tert*-Butylcarbonate (13a). To a stirred solution of **12** (0.52 g, 1.34 mmol) in MeOH (10 mL) was added pyridinium *p*-toluenesulfonate (0.17 g, 0.68 mmol). The mixture was stirred at room temperature for 15 h under N_2, after which H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with H_2O (70 mL) and brine (50 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (20% EtOAc/80% hexane) afforded the title product as a yellow oil (0.45 g, 80%). R_f (50% EtOAc/50% hexane) 0.59. IR, ν_{max} (film): 1757, 1704 (C=O). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.32 (s, 3H), 1.41 (s, 9H), 1.50 (s, 9H), 2.78 (dd, *J* 16.3, 8.9, 1H), 3.20 (m, 1H), 3.38 (s, 3H), 3.79 (m, 1H), 4.46 (d, *J* 10.2, 1H), 6.92 (d, *J* 2.2, 1H), 6.99 (s, 1H), 7.04 (d, *J* 2.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.19, 22.01, 28.70, 29.42, 35.39, 41.00, 57.44, 59.86, 61.35, 77.00, 80.21, 84.32, 120.21, 120.38, 130.92, 146.39, 150.76, 152.95, 157.64. FAB MS *m/z* (%): 422 (35), 322 (20).

2-Amino-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (13b). To a stirred solution of **13a** (0.42 g, 1.00 mmol) in DCM (5 mL) was added trifluoroacetic acid (0.7 mL, 9.96 mmol) dropwise. The mixture was allowed to stir for 15 h before removal of the solvent in vacuo in the presence of toluene (0.5 mL) to form an azeotrope with TFA. Purification of the residue by column chromatography (8% MeOH/91% DCM/1% NH_4OH) afforded the title product as a colorless oil (0.13 g, 59%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.15. IR, ν_{max} (film): 3392, 3350 (N−H), 3294 (O−H). ^1H NMR (270 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.38 (s, 3H), 2.56 (dd, J 15.4, 9.9, 1H), 2.84 (d, J 9.9, 1H), 3.22 (dd, J 15.4, 5.5, 1H), 3.37 (m, 1H), 3.46 (s, 3H), 6.61 (dd, J 8.2, 2.5, 1H), 6.78 (d, J 2.5, 1H), 6.88 (d, J 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.22, 27.49, 33.56, 40.00, 56.13, 60.25, 77.00, 112.79, 113.58, 122.82, 129.61, 145.16, 154.56. FAB MS *m/z* (%): 222 (100). HRMS ($C_{13}H_{20}NO_2$) calcd 222.1494, found 222.1506. Anal. ($C_{13}H_{19}NO_2 \cdot HCl \cdot 1.5H_2O$) C, H, N.

3-Methoxy-1,1-dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]-amino}-1,2,3,4-tetrahydronaphthalen-7-ol (14). To a stirred solution of **13b** (69 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (3 mL) was added *trans*-cinnamaldehyde (0.05 mL, 0.37 mmol). The reaction mixture was stirred for 15 h at room temperature after which time the solvent was removed in vacuo. The residue was redissolved in anhydrous MeOH (8 mL), and the solution was cooled to 0 °C. Sodium borohydride (50 mg, 1.23 mmol) was added portionwise over 1 h, and the resulting mixture was stirred for a further 15 h at room temperature. The reaction was quenched by the dropwise addition of 1 M HCl (5 mL), and the solution was adjusted to pH 7 with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. Column chromatography (3% MeOH/96% DCM/1% NH_4OH) afforded the title product as a colorless oil (86 mg, 82%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.26. IR, ν_{max} (film): 3327 (O−H). ^1H NMR (270 MHz, $CDCl_3$): δ1.18 (s, 3H), 1.38 (s, 3H), 2.57−2.71 (m, 2H), 3.25 (m, 1H), 3.48 (s, 3H), 3.50−3.54 (m, 1H), 3.73 (dd, J 13.6, 6.2, 2H), 6.33 (m, 1H), 6.54 (m, 1H), 6.61 (dd, J 8.2, 2.5, 1H), 6.78 (d, J 2.5, 1H), 6.90 (d, J 8.2, 1H), 7.26 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$): δ12.73, 19.72, 24.82, 26.61, 33.28, 39.54, 52.43, 55.17, 65.43, 77.00, 111.70, 112.17, 122.78, 124.67, 125.64, 126.89, 127.61, 128.39, 129.53, 135.88, 145.02, 152.98. FAB MS *m/z* (%): 338 (80). HRMS ($C_{22}H_{28}NO_2$) calcd 338.2120, found 338.2119.

Molecular Modeling. Structures **4a** and **9k** were drawn using the Builder option in MOE (version 2004.03; Chemical Computing Group Inc.) and minimized using the MMFF94x force field. The Flexible Alignment function was used for the overlay, with the Restraints command ensuring that the phenolic rings remained aligned.

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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